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ANNALS of SURGERY

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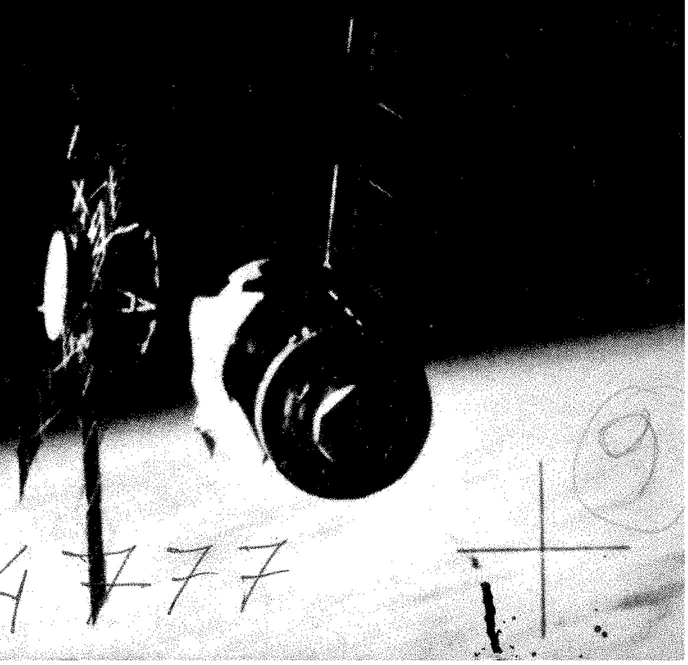

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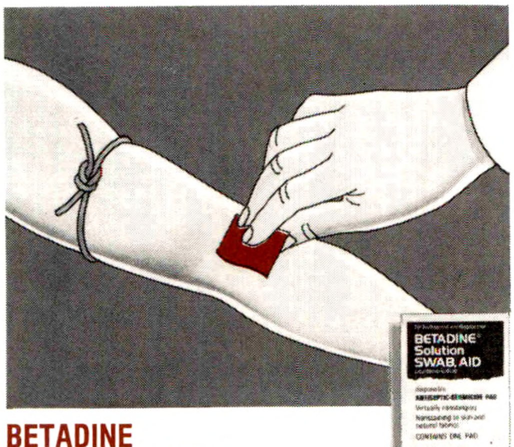
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Warnings: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions. Vacuolization has been reported, with a symmetrical, rostrocaudal distribution in the brainstem reticular formation of premature infants of low birth weight, especially those with skin rashes and wounds, who were washed with 3% hexachlorophene. However, the clinical correlates of such vacuolization have not been established since these infants also had critical clinical conditions or pathologic findings of independent etiology.

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In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin, or exposure to a powder accidentally containing approximately 6.5% hexachlorophene.

Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only*. If swallowed, pHisoHex is harmful, especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precautions: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

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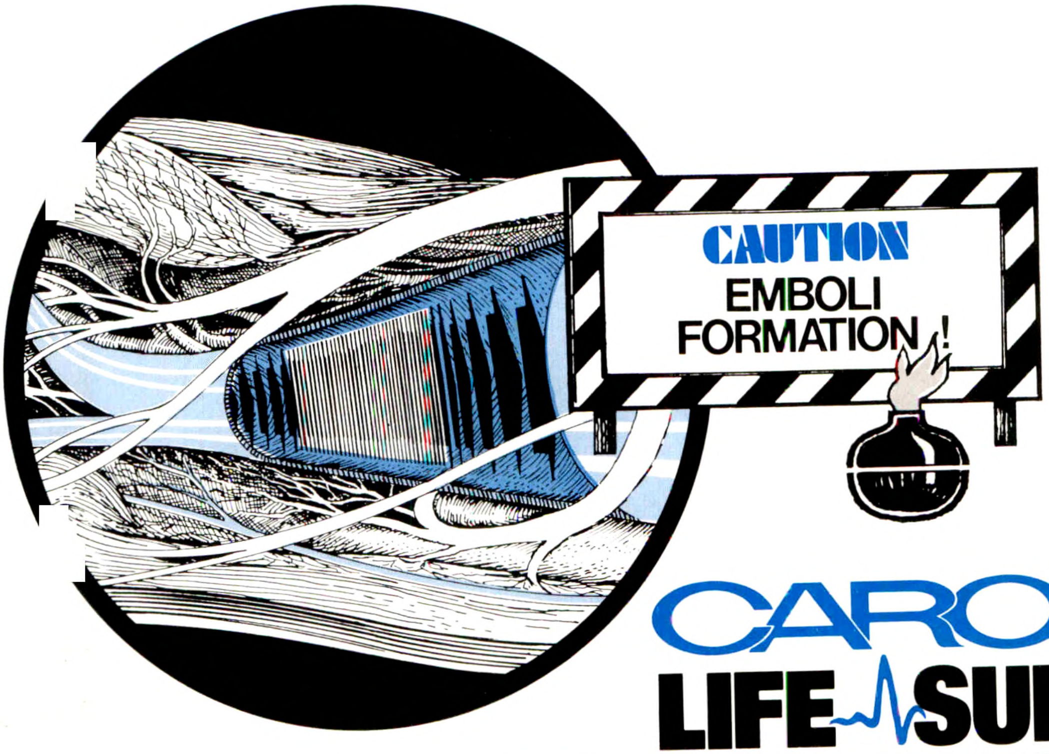

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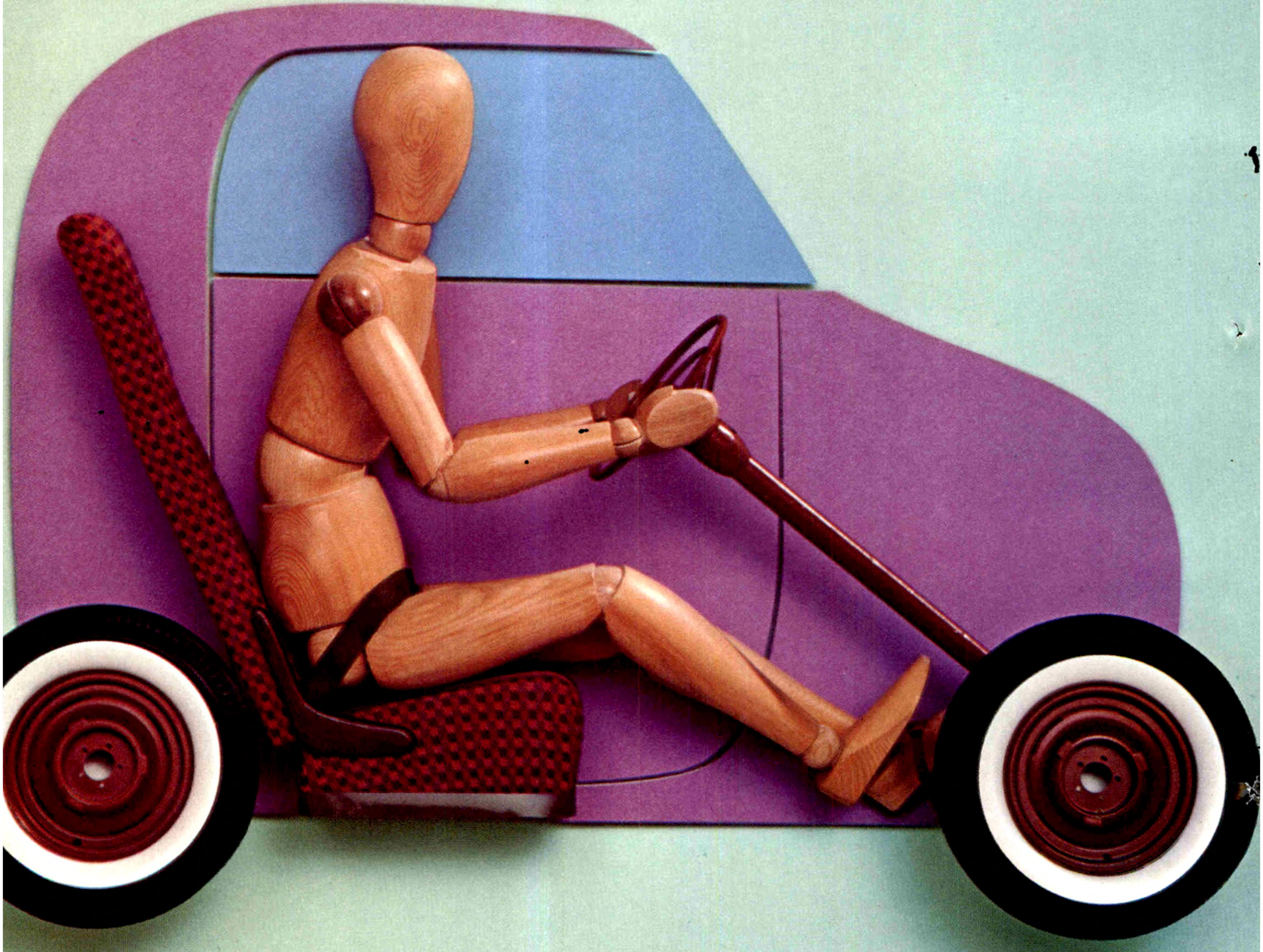

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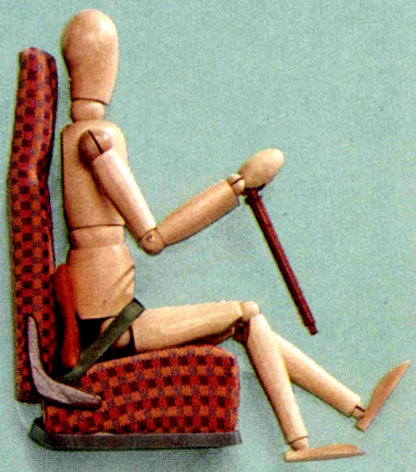

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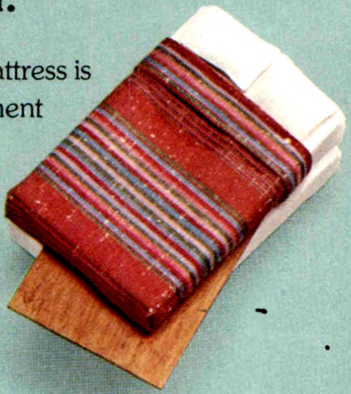

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Histochemical Changes in Gastric Mucosubstances in Patients with Acute and Chronic Ulcer Disease

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The several types of epithelial cells in human gastric mucosa produce different mucosubstances. The surface epithelium largely forms a neutral mucosubstance except that in about two-thirds of the specimens the deep foveolar cells produce a slight to moderate amount of a mucosubstance apparently containing sulfate esters and carboxyl groups. Mucous neck cells often exhibit a neutral mucosubstance but in about one-half of the stomachs reveal a slight to moderate reactivity indicative of sulfated mucosubstance. Chief cells contain a sulfated mucosubstance with unique histochemical properties. Mast cells vary widely in prevalence but those in the gastric mucosa appear depleted of stored mucosubstances when compared with those in the gastric submucosa or the esophagus. The sulfated mucosubstance normally abundant in human as in canine chief cells appears consistently depleted in patients with stress ulcer or hemorrhagic gastritis. In addition, mucus often appears depleted in the surface epithelium and interstitial edema is present in the superficial mucosa of these patients. These findings appear consistent with the view that biosynthetic activity in chief cells and surface epithelial cells is impaired perhaps secondary to shock-induced circulatory changes in gastric mucosa of patients with stress ulcer or hemorrhagic gastritis.

CHANGING CONCEPTS regarding the etiology of ulcerative diseases of the gastric and duodenal mucosa have been described in recent years. Chronic duodenal ulcer is generally considered to result from an acid hypersecretory state. Indeed, basal acid production and response to histamine stimulation are usually elevated above normal values in patients with this lesion.[8] An increase in the parietal cell population has also been demonstrated in patients with duodenal ulcer,[15] and correlation between acid output and parietal cell mass has been well documented.[1] The etiology of both chronic gastric ulcer and of "acute ulceration" of the stomach or duodenum is less well understood. Hypersecretion of acid is usually not a feature of chronic gastric ulcer disease,[8] and, excepting the "Cushing's" ulcer, it does not appear to be a predominant factor in acute ulcerations.[6] In such ulcerative conditions where gastric acid hypersecretion has not been clearly implicated, several theories as to the etiology have been proposed. A change in the mucous protective barrier has been suggested as a basis for such ulceration. An alteration in this barrier might result from decreased mucous production or a change in the character of the mucus produced, thereby rendering the gastric mucous membrane more susceptible to damage. Attempts to confirm this theory have been hampered by difficulties in accurately collecting and measuring gastric mucus. Histochemical techniques [18,19] provide a means of studying directly the cells of the gastric mucosa that produce the mucous protective barrier. The purpose of the present study is to evaluate with histochemical methods the mucosubstance present in the various gastric epithelial cells and to correlate the content of mucosubstance with acute ulcerative diseases of the gastric mucosa.

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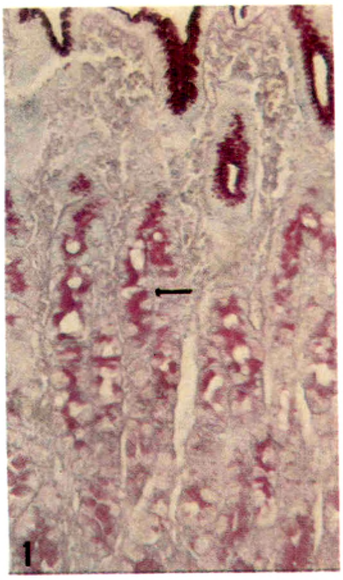
Materials and Methods

Portions of human stomach removed surgically were placed in a 2% calcium acetate, 10% formalin fixative as rapidly as possible and fixed for 24 hours prior to routine dehydration, embedding in paraffin and sectioning. Specimens included for study consisted of a moderately extensive segment of gastric corpus with no gross pathologic involvement as well as areas of grossly evident erosion, ulceration or hemorrhage.

Thirty-three specimens in which a sufficiently representative sample of gastric mucosa was available for examination and in which the pathologic diagnosis was established, were examined in the study. These specimens included nine patients with gastric ulcer, 16 with duodenal ulcer, five with stress ulcer and three with hemorrhagic gastritis. In the last group the hemorrhagic gastritis was associated with excessive intake of aspirin, uremia or an alcoholic debauch. The stress ulcer category included patients that had not been on steroids and who had sustained no central nervous system or thermal injury.[7] Stomachs from patients with Curling's ulcer, Cushing's ulcer and steroid-induced ulceration were examined but were not available in sufficient numbers to evaluate in this study.

Sections of each specimen were stained with hematoxylin and eosin for morphologic examination and with histochemical methods for visualizing and differentiating carbohydrate secretions of the stomach. The histochemical methods included the alcian blue pH 2.5-periodic acid Schiff (PAS) method of Mowry and Winkler, a sequence of aldehyde fuchsin or high iron diamine followed by alcian blue at pH 2.5 and azure A at pH 4.5.[17] The surface epithelium and mucous neck cells were evaluated particularly with the alcian blue-PAS sequence which colors neutral mucosubstance red and acid mucosubstance blue-purple to turquoise. The chief cells were appraised mainly with the aldehyde fuchsin-alcian blue sequence which stains sulfated mucosub-

FIG. 1. Mucosa from distal gastric corpus of a patient with a duodenal ulcer. Staining of mucus in the superficial and foveolar surface epithelium at the top exceeds that in the mucous neck cells (arrow) which, in turn, are stained darker than the weakly reactive zymogen cells at the bottom. The red staining provides an initial indication of a neutral mucosubstance. However, such staining may be encountered in secretions that have a low concentration of acid groups or in those that contain an acid mucosubstance which lacks affinity for alcian blue as does the sulfated mucosubstance of the chief cells or some mucous neck cells (cf. Figs. 5–7). The stained mucosubstance here presumably exemplifies the normal storage of secretion as it resembles in amount that generally found in normal animal stomachs. Alcian blue-PAS, ×100. FIG. 2. Mucosa of gastric corpus from patient with duodenal ulcer. This more tangential section differs from that in Fig. 2 in the abundance of secretion accumulated in the superficial and foveolar surface epithelium and relative scarcity and weak staining of subjacent mucous neck cells. Increased secretion in surface epithelium was not a constant finding in these patients, however. The mucous neck cells about equal in number those usually observed in the anterior region of the corpus. Alcian blue-PAS, ×100. FIG. 3. Mucosa from the body of the stomach of a patient with stress ulcer. The superficial and foveolar epithelium are largely depleted of mucous secretion. A few cells deep in the mucosa show spare apical secretion (arrows) and are probably deep foveolar cells. Zymogen cells at the bottom lack appreciable staining. Alcian blue-PAS, ×100. FIG. 4. Superficial mucosa from the corpus of the stomach of a patient with gastric ulcer. Purple-blue staining indicative of acid mucosubstance containing carboxyl and sulfate groups is evident in the deep foveolar epithelium (arrow) and, to a lesser extent, in the superficial surface epithelium. Such foveolar basophilia was observed in about a third of the specimens but appeared unrelated to disease states. The purple staining indicates sulfated mucosubstance in the mucous neck cells below (cf. Figs. 6, 7). Aldehyde fuchsin-alcian blue, ×100. FIG. 5. Mucosa from the corpus of the stomach of a patient with gastric ulcer. This is a somewhat tangential section at the level of the mucosa that contains mucous neck cells and zymogen cells. The mucous neck cells exhibit characteristic PAS reactivity (arrows), but despite the presence of acid groups evidenced by their affinity for aldehyde-fuchsin (cf. Fig. 6), lack alcianophilia and stain red like neutral mucosubstance. Alcian blue-PAS, ×100. FIG. 6. Section adjacent to that in Fig 5. Purple staining indicative of sulfated mucosubstance is evident in the rather large mucous neck cells (arrows). Aldehyde fuchsin-alcian blue, ×100. FIG. 7. Mucosa of the corpus of the stomach from a patient with salicylate gastritis. (a) Purple staining of mucous neck cells (arrows) indicates sulfated mucosubstance. This staining contrasts with that of many mucous neck cells which stain strongly with the PAS method but lack affinity for any of the basic dyes that visualize acid mucosubstance (see Fig. 6 for another exception) and appear, therefore, to secrete neutral mucosubstance. The surface epithelium at the top, except for a few cells in the base of the pits, is unreactive and the zymogen cells at the bottom reveal only light staining (cf. with Figs. 8–12). Mast cells are not evident. (b) The stellate mucous-neck cells are filled with purple secretion and fit between unreactive parietal cells. Aldehyde fuchsin-alcian blue. (a) ×100 (b) ×400. FIG. 8. Mucosa from the corpus of the stomach of a patient with duodenal ulcer. Purple stained material rich in sulfated mucosubstance fills the chief cells in the deeper half of the mucosa. Surface epithelium lining the foveolar pits at the top and subjacent mucous neck cells lack such staining but scattered mast cells stain strongly. Aldehyde fuchsin-alcian blue, ×100. FIG. 9. Like Fig. 8. Heavy staining of chief cells at the bottom contrasts with lack of reactivity in surface epithelium, ×25. FIG. 10. Like Fig. 8. The granular secretion stains for sulfated mucosubstance occupying the apex of zymogen cells. Parietal cells are unstained. ×400. FIG. 11. Mucosa from the body of the stomach of a patient with stress ulcer. Chief cells lack stored secretion retaining a very few apical granules and a surface layer (short arrow) of mucosaccharide-rich substance. Parietal cells in demilunar position appear lighter (long arrow). ×400. FIG. 12. Like Fig. 11. Chief cells as well as most of the surface epithelium and mucous neck cells are unstained. Although the amount of secretion in chief cells varied in each clinical group, the patients with stress ulcer generally lacked secretion as here. A few surface epithelial cells at the base of the pits (arrow) stain moderately. Mast cells are not evident. Elastic fibers in the basal lamina propria stain strongly. Aldehyde fuchsin-alcian blue. ×100.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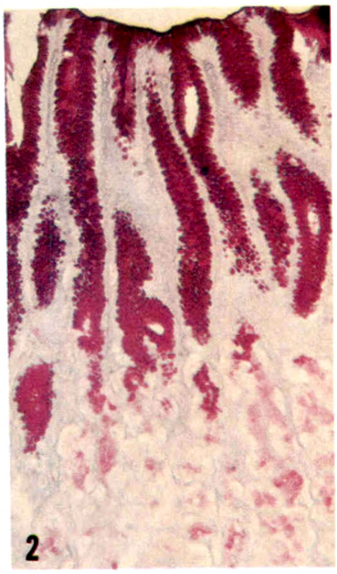
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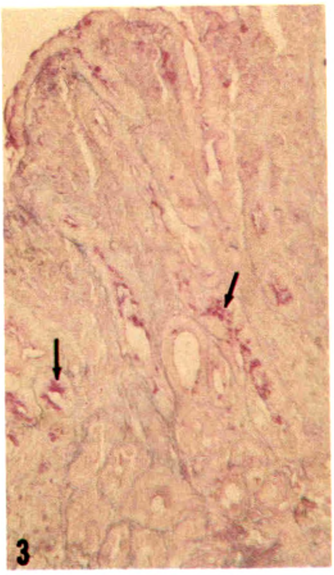
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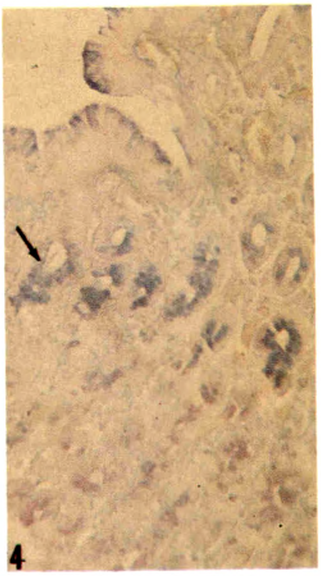
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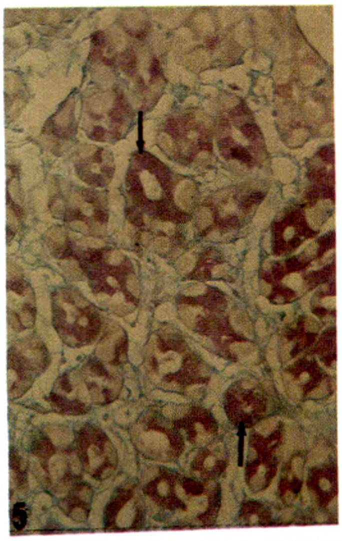
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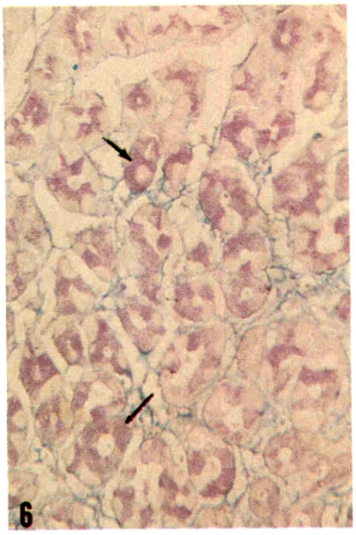
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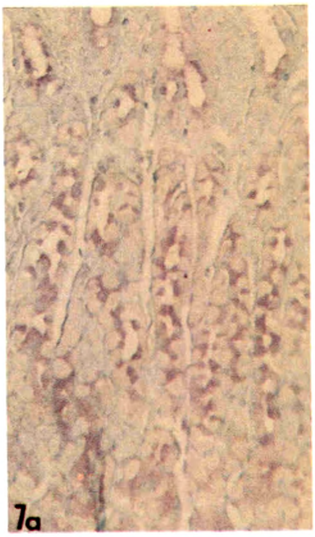
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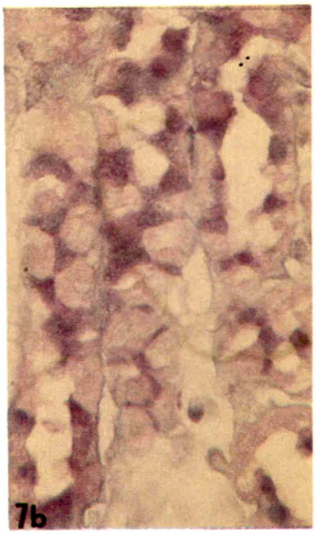
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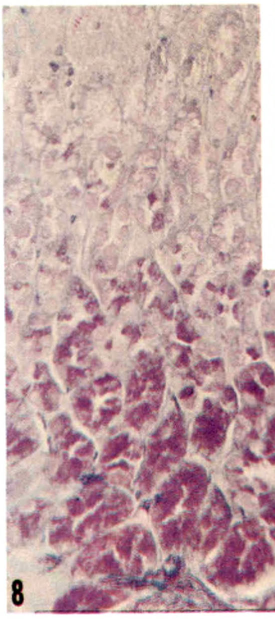
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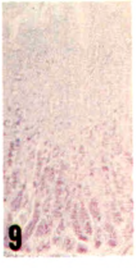
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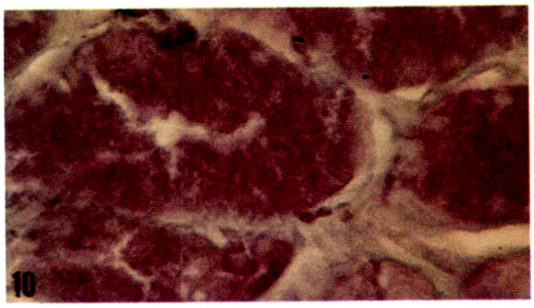
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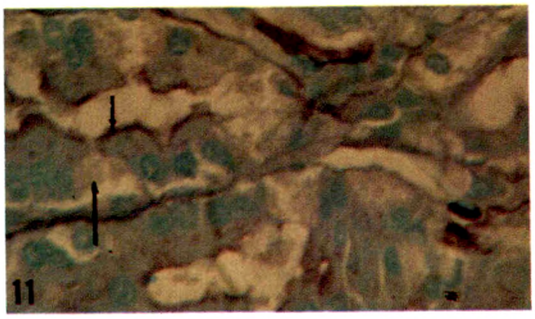
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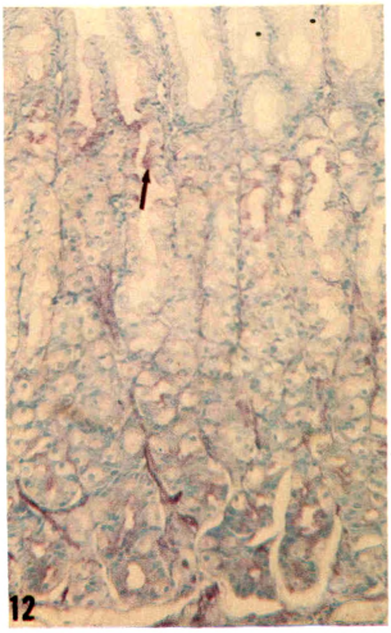
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stance purple. Mast cells were visualized with the aldehyde fuchsin, high iron diamine and azure A methods.

To evaluate pathologic variations, specimens were coded and the mucosubstance in the several cell types in each specimen was estimated subjectively without knowledge of the clinical diagnosis. The staining in each cell type with a given procedure was graded as either strong to intermediate or weak to absent. These semiquantitative values were then matched to the patient to determine whether an abundance or depletion of stored secretion characterized a particular disease process.

Results

Mucosubstance of the normal human stomach was difficult to assess because postmortem autolysis may alter the secretion in autopsy specimens, and surgical specimens were only available from patients with known gastric disease. An arbitrary decision was made that carbohydrate histochemistry of the stomachs from patients with duodenal ulcer probably provided the closest approximation to normal in our population. This decision was based partly upon the fact that such stomachs were very similar to normal canine stomachs[19] in the consistent strong staining of the chief cells for acid mucosubstance.

Duodenal Ulcer Patients

A. Surface Epithelium. The surface epithelium of the body of the stomach secreted mainly neutral mucosubstance as evidenced by the intense red coloration with the alcian blue pH 2.5-PAS procedure (Figs. 1, 2). Secretion in and on the surface epithelium largely failed to react with the alcian blue in this sequence and with the other basic dyes including aldehyde fuchsin, high iron diamine and azure A. However, about two-thirds of the stomachs disclosed light to moderately strong blue-purple staining with the aldehyde fuchsin-alcian blue method in a few to many of the foveolae at the base of the pit (see Fig. 4 for comparable staining). Such staining demonstrating acid mucosubstance was also evident in scattered small areas in the superficial surface epithelium in a few of the specimens.

All 16 of these patients had a moderate to large amount of the neutral mucosubstance in surface epithelial cells. Several of these stomachs disclosed a few to numerous areas in which abundant secretion filled foveolae and adhered to the luminal surface (Figs. 13, 14). The most superficial cells of the surface epithelium often lacked stored secretion in these foci, however, and cells lining these foveolae varied markedly in staining intensity (Figs. 13, 14). Whether such adherent luminal mucus and variable staining of surface epithelial cells were pathologic features remained uncertain for lack of surgical specimens without gastrointestinal disease.

B. Mucous Neck Cells. The mucous neck cells varied in number among different subjects and appeared more numerous in the distal than in the proximal corpus. These cells usually stained a moderately strong red indicative of neutral mucosubstance with the alcian blue-PAS sequence (see Fig. 5 for comparable reactivity), but occasionally were colored the purple or blue-purple indicative of acid mucosubstance. In nearly half of the cases, mucous neck cells revealed slight to moderate blue-purple coloration with the aldehyde fuchsin-alcian blue sequence indicating presence of mucosubstance with acid groups (see Fig. 6 for comparable staining).

C. Chief Cells. These cells evidenced an abundance of sulfated mucosubstance as demonstrated by their strong reddish-purple staining with the aldehyde fuchsin step of an aldehyde fuchsin-alcian blue sequence (Figs. 8–10). These zymogen granules possessed no affinity for the other basic dyes employed but displayed weak PAS reactivity (Figs. 1, 2). Their staining with aldehyde fuchsin remained unaltered after exposure to testicular hyaluronidase. The secretion in human chief cells thus resembled that in canine zymogen cells except the latter displayed weak to moderate affinity for alcian blue and for high iron diamine and lability to testicular hyaluronidase.[18,19]

The chief cells from 14 of the 16 patients with duodenal ulcer contained moderate to large amounts of the sulfated mucosubstance (Figs. 8–10). One of the two patients lacking this substance had consumed large quantities of alcohol and was actively hemorrhaging at the time of operation.

D. Mast Cells. Mast cells infiltrating the lamina propria throughout the corpus varied from sparse to very numerous in different stomachs in this group. The mast cells stained with high iron diamine (Fig. 19), aldehyde fuchsin, and azure A at pH 4.5. The mast cells in the lamina propria of the stomach (Figs. 19a, 19c), however, stained relatively weakly with all these procedures when compared to the mast cells in the submucosa (Figs. 19a, 19b) or in the esophageal wall.

Gastric Ulcer Patients

A. Surface Epithelium. Six of the nine specimens showed a moderate to large amount of neutral mucosubstance throughout most of the surface epithelium of the gastric corpus, although disclosing foci of depletion, particularly in areas bordering ulceration. In some such foci the storage of secretion in deep foveolar cells contrasted with the depletion of secretion in superficial cells (Fig. 15). Granular collections probably in the Golgi zone comprised the only cytoplasmic secretion in some apparently hypersecreting cells (Fig. 15). Three of these specimens revealed widespread depletion of surface epithelial mucosubstance, however. About a third of these stomachs exhibited blue-purple staining in deep foveolar cells with the aldehyde fuchsin-alcian blue method (Fig. 4).

B. Mucous Neck Cells, Chief Cells, and Mast Cells. The staining characteristics and quantity of mucosubstances in the mucous neck cells (Figs. 5, 6), chief cells and mast cells did not appear to differ consistently in the patients with gastric ulcer and in those with duodenal ulcer. Sulfated mucosubstance of the chief cells appeared depleted in two specimens in this group. However, these stomachs were from patients who had consumed large amounts of alcohol preoperatively and were actively hemorrhaging at the time of operation.

Stress Ulcer Patients

A. Surface Epithelium. Patients with stress ulcer disclosed a variable content of mucosubstance in the surface epithelium of the body of the stomach. This epithelium in three of these subjects revealed depletion of mucosubstance in small areas, particularly foci of acute erosion or ulceration (Figs. 16, 17), but disclosed a moderate amount of neutral mucosubstance throughout the intact epithelium elsewhere (Fig. 18). The other two specimens revealed marked, widespread depletion of this mucosubstance (Fig. 3). The amount of acid mucosubstance in the foveolar pits did not appear increased.

B. Mucous Neck Cells, Chief Cells and Mast Cells. No consistent difference between these specimens and those in the duodenal ulcer group was discerned in the character or amount of secretion in the mucous neck cells or in the prevalence of mast cells. The chief cells, however, were depleted of mucosubstance in all five of these specimens (Figs. 11, 12). The diminished chief cell affinity for aldehyde fuchsin varying from weak staining to virtual absence of reactivity appeared to be a consistent and striking change in this group.

Patients with Hemorrhagic Gastritis

A. Surface Epithelium. These specimens disclosed only small amounts of neutral mucosubstance in much of the superficial epithelium of the gastric corpus and revealed wide areas of total depletion. The secretion in deep foveolar cells did not differ consistently in these specimens and in those with duodenal ulcer.

B. Mucous Neck Cells, Chief Cells and Mast Cells. In the stomach of the patient with salicylate gastritis the mucous neck cells appeared numerous and large and contained abundant secretion with relatively strong affinity for aldehyde fuchsin indicative of sulfated mucosubstances (Fig. 7). All three of these stomachs exhibited very weak or no staining for sulfated mucosubstances in the chief cells.

In all stomachs of this and the stress ulcer groups, increased stromal area which stained only faintly with all of the methods, separated the more superficial portion of the glands widely (Figs. 17, 18). These areas of presumed interstitial edema were widespread and diffuse in some patients and restricted to bullous-like foci in others. This change was not evident in the gastric and duodenal ulcer groups except that loose superficial stroma suggestive of edema was observed in a duodenal ulcer patient who was in active hemorrhage at the time of operation.

At the outset of this study, little attention was paid to the antral portion of the stomach. More recently, investigation of this area has shown the surface epithelium to contain neutral mucosubstance, the amount of which paralleled that found in the body of the stomach in the various disease categories.

Discussion

The mucin histochemistry of the gastric mucosa of patients undergoing surgery for peptic ulcer or neoplastic disease of the stomach has been described previously.[9,21] These studies have shown, as has been confirmed here, that several types of gastric epithelial cells produce different mucosubstances. Thus, the superficial epithelial cells and pyloric glands contain neutral mucosubstances staining strongly with the PAS method. Sulfated mucosubstance has previously been referred to as variably present in human chief cells.[21] The present studies largely confirm these previous observations but differ in some respects. In particular, they disclose that, although the deep foveolar cells may produce neutral mucosubstance, they more often form an acid mucosubstance which, from the blue-purple staining with the aldehyde fuchsin-alcian blue sequence, apparently contains both sulfate and carboxyl groups. The present observations also indicate that the mucous neck cells more commonly produce neutral mucosubstance but in about one-third of the patients of all categories form a mucosaccharide with sulfate and possibly also carboxyl groups as indicated by purple staining with aldehyde fuchsin-alcian blue method. The very marked accumulation of sulfated mucosubstance in mucous neck cells of the patient with salicylate gastritis warrants further investigation to determine whether this change may constitute a characteristic aspect of this disease. The demonstration of sulfated mucosubstance in chief cells (Figs. 8–10) and the assessment of this mucosaccharide in several clinical groups document it as a prominent and constant component of chief cells in the human stomach.

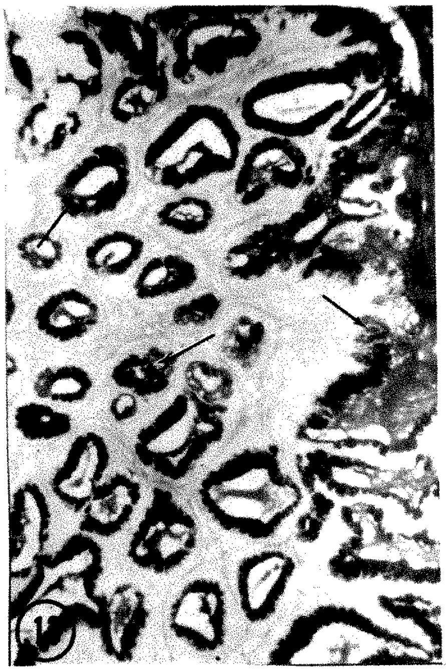
Attention has been directed toward the gastric mucous protective barrier in those gastric diseases in which the etiology cannot be directly related to the hypersecretion of gastric acid. Menguy demonstrated a decrease in production of mucus in the stomachs of dogs receiving intramuscular cortisone. He proposed that the decreased mucus resulted from steroid administration and was at least a part of the underlying cause of "steroid ulcers."[12] He also found that aspirin caused a decrease in the rate of gastric mucous secretion and suggested that hemorrhagic gastritis from aspirin and other ulcerogenic agents may be secondary to a defective mucous barrier. Menguy subsequently postulated that stress ulcer with a similar histopathological picture may be due to alterations in the mucus protective barrier.[13] Presumably this protective barrier consists primarily of the secretion of the surface epithelium. Histochemical studies consistent with this thesis have delineated the carbohydrate histochemistry of the normal canine gastric mucosa,[18,19] and have shown striking changes in the mucous-producing cells in sham-fed dogs receiving large doses of corticosteroids.[20] The resultant erosions and superficial ulcerations were associated with focal depletion of mucus and goblet-like hyperplasia in the surface epithelium and widespread depletion of the sulfated mucosubstance in the chief cells.

The "acid back-diffusion" theory proposed originally by Davenport postulated that a defect in the gastric mucosa rather than acid hypersecretion was important in the development of gastric ulcers.[3] His extensive studies demonstrated that bile, aspirin and urea among other agents caused a breakdown in the mucous protective barrier and allowed back-diffusion of hydrochloric acid.[4,5] Skillman and colleagues demonstrated acid back-diffusion in rabbits subjected to hemorrhagic shock. This phenomenon was measured in critically ill patients in whom acute ulcerations were likely to occur.[16] These authors and Wlodeck [22] have proposed that, as a consequence of poor vascular perfusion, the mucous protective barrier is altered in such a way that hydrochloric acid diffuses back into the mucosa and causes ulceration.

On the other hand, recent analyses of aspirated gastric mucous secretion have suggested that production of mucus is not decreased in stomachs of patients with severe trauma and hemorrhagic shock.[11,14] However, the obvious problem of relating mucus aspirated from the lumen to the mucus that fills and coats the surface epithelial cells would seem to question whether or not these analyses on aspirated secretions demonstrated a uniform lack of change in the mucous barrier in patients with bleeding ulcer. Moreover, the observation that luminal mucus is not decreased seems inconsistent with microscopic observations of focally depleted mucus, particularly in the areas of acute ulceration.[11] Cytochemical observation, although limited in scope and semiquantitative in nature, affords the more direct view of the mucous barrier provided by the surface epithelium allowing, in particular, appraisal of focal changes in mucus in or on the surface epithelium.

From the results of this study the gastric epithelium of patients with stress ulcer or hemorrhagic gastritis differs from that of patients with gastric or duodenal ulcer. Moderate to large amounts of mucosubstances in the surface epithelial cells as well as the chief cells characterized the latter except for focal depletion of the surface epithelium in the areas of chronic gastric ulcerations. Specimens from patients with stress ulcer and hemorrhagic gastritis, on the other hand, showed depletion of the surface epithelial secretion in most cases.

Fig. 13. Superficial mucosa from the gastric corpus of a patient with duodenal ulcer. Surface epithelium shows hypersecretion of (red) stained mucus which adheres to the luminal surface on the right and fills some pits. Some epithelial cells (arrows) stain lighter than others. ×100. Fig. 14. Superficial mucosa from the body of the stomach of a patient with duodenal ulcer. The lumen (L) of several foveolar pits encloses abundant mucus which is continuous with mucus on the surface out of the field toward the right. The surface epithelium stores abundant secretion in an apical goblet-like mass. The staining of stored secretion varies from very intense in some cells, to relatively light in others (arrows). Alcian blue-PAS, ×100. Fig. 15. Superficial mucosa from the body of the stomach of a patient with gastric ulcer. Moderately stained mucous material adheres to the luminal surface at the right. The surface epithelium lining the foveolae retains stored secretion (arrows). The more superficial surface epithelium appears hyperplastic and, although lacking abundant stored secretion, exhibits small, well-stained particles which underlie a vacuolated apical stratum. These particles, with their red staining demonstrative of neutral mucosubstance, apparently occupy the Golgi area and indicate active synthesis of mucosubstance in cells which, retaining little mucus, possibly secrete at an increased rate. Alcian blue-PAS, ×250. Fig. 16. Mucosa of gastric corpus of patient with stress ulcer. A thin layer of fibrin covers the surface in this focal area of erosion. Although absent superficially the surface epithelium with stored mucosubstance lines the foveolae. Mucous neck cells (arrows) contain scant secretion and zymogen cells basally appear unstained. Alcian blue-PAS, ×100. Fig. 17. Mucosa from the distal portion of the body of the stomach in a patient with stress ulcer. The superficial surface epithelium at the top lacks mucous secretion in contrast to that of the subjacent pits. Mucous neck cells with heavily stained, abundant secretion extend to the bottom of the gastric glands and zymogen cells are scarce. Although mucous neck cells are normally more abundant in the distal corpus they rarely disclose such deep extension. The superficial stroma appears edematous. Alcian blue-PAS, ×100. Fig. 18. Mucosa in the body of the stomach of a patient with stress ulcer. Secretion in the superficial and foveolar surface epithelium does not appear altered. Stroma that is more lucent than in normal or in other pathologic stomachs—presumably as a result of edema—surrounds and separates widely the foveolae in the most superficial mucosa but not the glands in the deeper portion (cf. Figs. 12–14). Alcian blue-PAS, ×100. Fig. 19. Gastric corpus from a patient with duodenal ulcer. (a) Mast cells in the mucosa at the right appear smaller and exhibit less of the (purple-black) staining for sulfated mucosubstance compared with mast cells in the muscularis mucosa or submucosa toward the left. (b) Enlargement of a submucosal area in stomach shown in Fig. 19a. The mast cells here appear larger and contain more sulfated mucosubstance than do those in the mucosa. Such differences characterized mast cells in these two locations in most of the specimens examined. (c) Enlargement of a mucosal area in stomach shown in Fig. 19a. High iron diamine stain. (a) ×250 (b) ×1000 (c) ×1000.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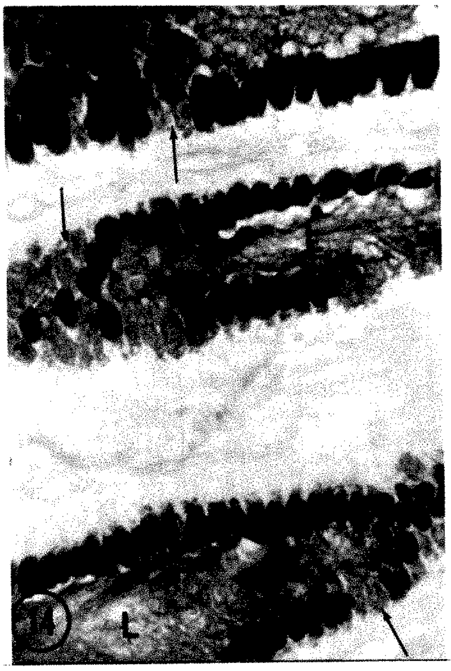
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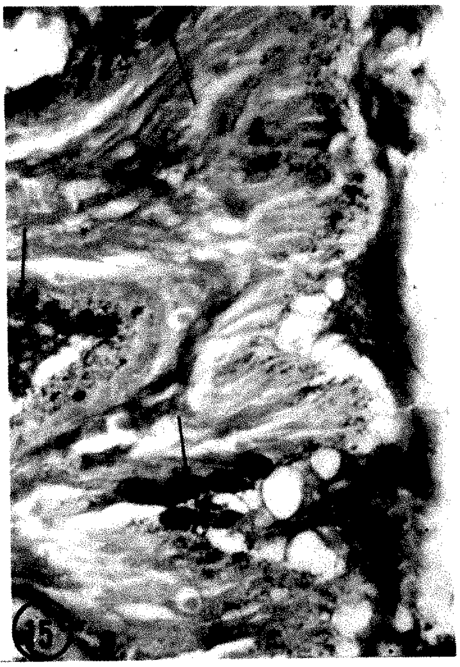
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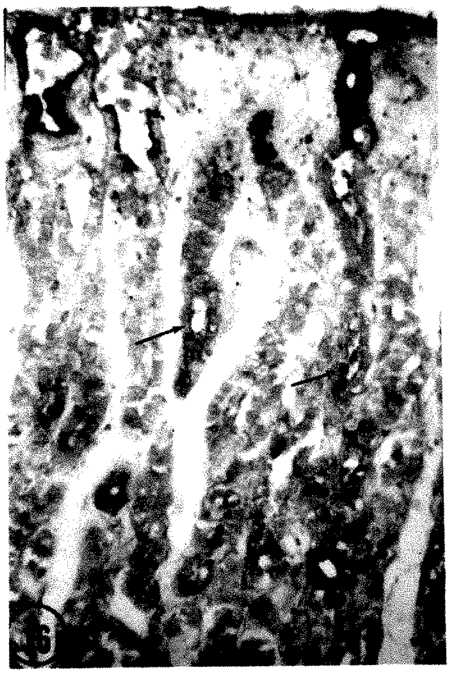
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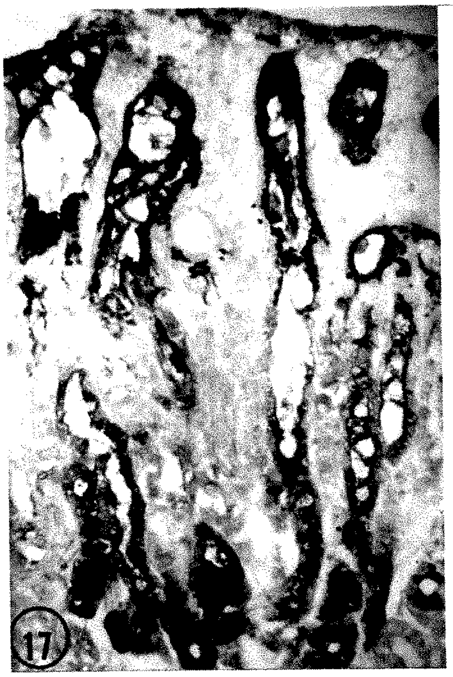
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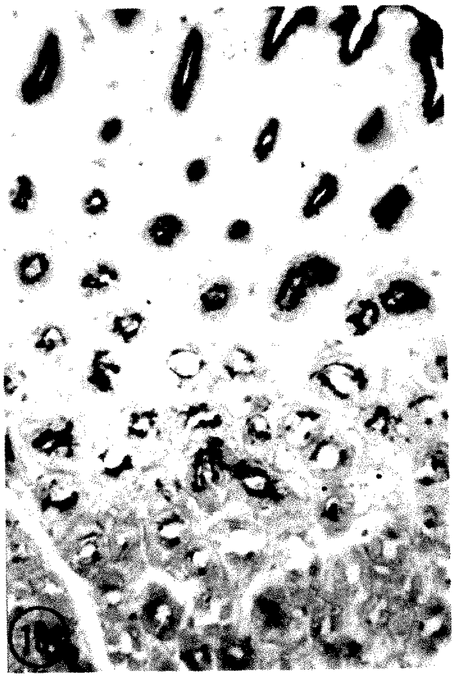
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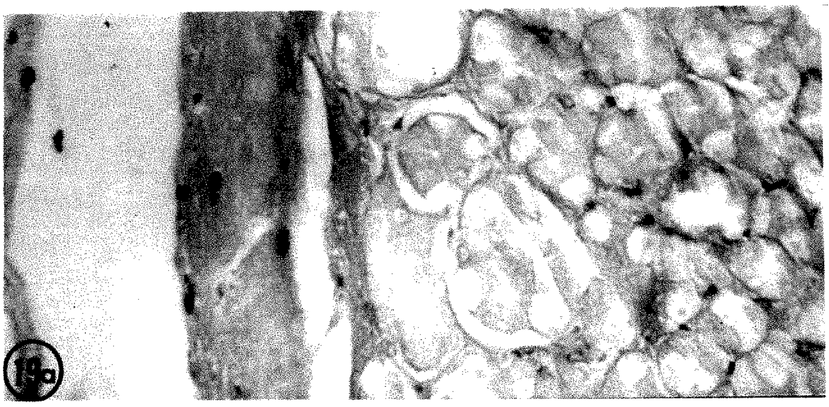
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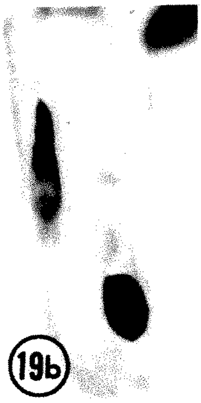
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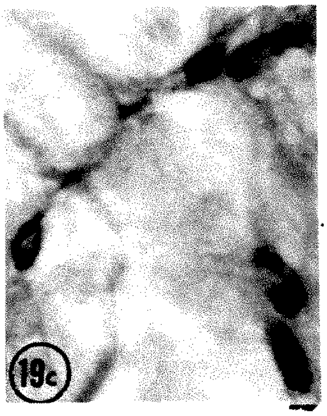
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Mucosubstance of the chief cells appeared depleted in all patients with stress ulcer or hemorrhagic gastritis. Lack of this secretion would very likely impair resistance of the gastric epithelium to peptic digestion, since sulfated mucopolysaccharides are known to inhibited pepsin.[2,10] The present observations have not demonstrated, however that the chief cell mucopolysaccharide was decreased relative to pepsin in the pathologic groups. The few patients in the duodenal and gastric ulcer categories who revealed depletion of mucosubstance in the chief cells had been actively bleeding at the time of operation and gave a history of excessive alcohol intake. Because of the hemorrhage a condition of shock comparable to that in the other groups may have prevailed in these patients. The observed absence of mucosaccharides in both the surface epithelium and the chief cells possibly reflects impaired biosynthetic activity rather than accelerated secretion. The mucosaccharide-producing cells of the gastric mucosa may then be sensitive to "low perfusion states" which result from the shunting of blood away from the gastric mucosa in conditions of shock. As the ability to produce the mucous secretion is either reduced or exhausted by impaired biosynthesis, the protective barrier presumably fails and acid back-diffusion occurs, resulting in erosions or acute ulcerations.

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Use of Elemental Diets to Correct Catabolic States Prior to Surgery

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An elemental diet was used to prepare 11 severely debilitated malnourished patients for operation. Indications included: 1) as a substitute for parenteral hyperalimentation when catheter sepsis occurred with the latter; 2) high small fistulae; 3) short bowel syndrome; 4) radiation enteritis; and 5) partial obstruction of the gastrointestinal tract. All patients were converted to a positive nitrogen balance as evidenced by a substantial gain in weight and in serum albumin levels. All tolerated corrective operations without difficulty and their wounds healed per primum.

THE IMPORTANCE of correcting catabolic states prior to operation has been well appreciated. The patient who is unable to ingest an adequate diet taxes the ingenuity of the surgeon. Intravenous feeding proved to be a helpful but inadequate solution for many years. Parenteral hyperalimentation was a major advance in providing adequate nutritional support to cachectic patients prior to operation. Dudrick and associates[4] demonstrated that this would not only supply all essential nutrients required for normal growth and development but would allow reversal of the catabolic states associated with various debilitating disease states. We also found parenteral hyperalimentation to be a very valuable tool in the management of preoperative and postoperative nutritional problems. Unfortunately, we have encountered complications with some patients which contraindicated the use of parenteral hyperalimentation. The purpose of this report is to describe our experience using an elemental diet in the preparation of a select group of patients for surgery. Since this was given orally it avoided the complications of prolonged intravenous alimentation. Furthermore, in the majority of patients it was less confining and it simplified and reduced the nursing care required.

Stephens and Randall[6] have emphasized the therapeutic value of a chemically defined elemental diet in the nutritional management of a select group of patients in severe catabolic states, who have a functional or partially functional gastrointestinal tract.

Elemental diets of this nature are almost totally absorbed in the proximal small intestine, leaving little residue to reach the colon. By significantly reducing fecal medium, the diet changes the quality and reduces the quantity of microflora found in the normal bowel. Because of their elemental nature and low fat content they have the advantage of being relatively non-stimulating of pancreatic, biliary and gastrointestinal secretions.[2,5] They have the additional advantage of storage in a powdered form and ease of reconstitution and administration without special equipment.

Most reports have stressed the use of these diets in the management of postoperative catabolic states complicated by intestinal fistulas and malabsorptive states.[3] Buonos[1] has shown that elemental diets are well absorbed by intestinal epithelium damaged by radiation or by 5-Fluorouracil, and has shown the salutory effect of an elemental diet on the course of acute pancreatitis.[7]

Eleven patients in a severely debilitated and malnourished state, as evidenced by extensive loss of lean tissue and low serum albumin levels, were supported exclusively on an elemental diet delivered orally or via a feeding tube for a period of three or more weeks. This group of patients were considered poor surgical candidates primarily on the basis of their nutritional status and had failed to respond to conventional nutri-

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TABLE 1. *Composition of Elemental Diet Vivonex High Nitrogen* (per 1000 ml of 25 per cent weight per volume)*

		Vivonex High Nitrogen
Calories	kcal	1000
Carbohydrate	gm	203
Amino acids	gm	45.5
Nitorgen	gm	7.2
Fat	gm	0.44
Sodium	mEq	33.5
Potassium	mEq	23
Choloride	mEq	52.5
Magnesium	mEq	13.3
Calcium	mEg	4.3

* Eaton Laboratories.

tional methods. In two cases parenteral hyperalimentation was begun but had to be discontinued because of recurrent septicemia of catheter origin.

Table 1 gives the composition of the elemental high nitrogen diet used. This supplied 7.2 gm nitrogen or 45 gm of amino acids per 1000 ml of solution. If the patient could tolerate a small feeding tube, the diet was given via tube using a Barron pump continuously over 24 hours. An attempt was made to deliver about 3000 ml per day in the hope of providing 3000 calories. The diets were flavored and some patients were able to drink the desired volume in 24 hours. However, most often the feeding was accomplished through a small #10 French nasogastric feeding tube or via a gastrostomy tube with the constant infusion pump. The intragastric drip was begun at 40 ml/hour and then was increased progressively by 500 to 1000 ml per day over 5 days up to the desired volume.

The patient's intake and output and body weight were monitored. Urinary glucose, acetone and specific gravity were checked every six hours and regular insulin was given as necessary to control significant glycosuria. Prothrombin time levels were also assayed and, if necessary, vitamin K was given. Plasma total protein and plasma albumin and body weight were used as objective criteria of correction of the catabolic state.

Results

Eleven patients were supported exclusively on a chemically defined elemental diet prior to surgical interven-

TABLE 2. *Summary of Patients Receiving Elemental Diet*

Patient Chart # Age and Sex	1° Pathology	Surgery	Indications	Elemental Diet-Preop. Therapy	Maximum	Pre-Diet Wt. TP/A*	Post-Diet Wt. TP/A*
Case 1 30–79–22 69—M	Ca. cervical esophagus	S/P cervical esophagostomy Thyroidectomy Parathyroidectomy Laryngectomy Rt. colon interposition	malnutrition	3 weeks	3000 ml	198/3.0	209/3.5
Case 2 30–49–31 54—F	Ca. midesophagus	Irradiation Rt. colon interposition	malnutrition	5 weeks	3000 ml	89/2.5	101/3.3
Case 3 30–15–53 64—M	Ca. midesophagus	Irradiation	malnutrition	5 weeks	3000 ml	106/2.4	125/3.0
Case 4 69—M	Dysphasia following CVA Sacral decubitus	Debridement	cachexia	4 weeks	2500 ml	91/2.0	96/2.7
Case 5 11–03–61 74—F	Granulamtous colitis	Total colectomy & ileostomy	fistula	3 weeks	2500 ml	119/1.9	125/2.7
Case 6 29–88–27 68—M	Sigmoid diverticulitis Enterocolic fistula Intra-abd. abscess	S/P transverse colostomy Drainage intra-abd. abscess Resection S.B. Fistula-entero enterostomy	fistula	3 weeks	3000 ml	136/1.8	145/2.8
Case 7 28–76–36 24—M	S/P auto accident multiple facial fractures & thoracic trauma	Tracheostomy Insertion chest tube Decortication rt. lung	malnutrition	4 weeks	4000 ml	156/2.11	160/2.9
Case 8 21–58–39 49—F	Papillary adenoca. rt. ovary Radiation enteritis	S/P/ TAH Resection of colo-cutaneous fistula	obstruction	16 weeks	1200 ml	116/2.6	129/3.1
Case 9 15—F	Regional enteritis S/P ileo colectomy & Jejuno-desc. colostomy	Resection of colo-cutaneous fistula	fistula	5 weeks	1500 ml	59/2.9	68/3.2
Case 10 72—F	Peptic esophageal stricture	Bouginage side-to-side esophage-gastrostomy	obstruction	12 weeks	3000 ml	72/2.0	88 /2.8
Case 11 68—M	Gastric outlet obstruction S/P subtotal gastrectomy BII & stomal malfunction	Conversion to BI	obstruction	5 weeks	3500 ml	74/1.8	90/2.9

* Total Protein/Albumin.

tion. Table 2 lists the primary pathology leading to their debilitation and summarizes their hospital course. All patients failed to maintain or gain weight with conventional nutritional methods. Serum albumin and hemoglobin values fell to subnormal levels and were often associated with electrolyte imbalances.

Figure 1 shows the pattern of weight gain in five patients illustrating an initial lag period during the first week, a period of rapid acceleration of weight again during the second and third weeks followed by a plateau phase.

Figure 2 demonstrates the changes in serum albumin in all patients at the end of a three week period of therapy. Serum albumin levels increased between 0.5 and 1.0 gm per 100 ml. This was found to be statistically significant and is an indication that positive nitrogen balance was achieved.

The indications for the use of an elemental diet in this group were: 1) catheter sepsis; 2) small bowel fistula; 3) short bowel syndrome; and 4) esophagogastric obstruction. Most of our patients had more than one of these indications.

The following case reports illustrate our indications for the use of the elemental diet.

Case Reports

Case 9, catheter sepsis: This 15-year-old female with a four-year history of regional enteritis refractory to medical therapy underwent an ileocolectomy and jejuno descending colostomy in November 1972 leaving her with only 8 feet of small bowel. Postoperatively she developed an anastomotic leak and generalized peritonitis. At the time of drainage there was some injury to the small bowel resulting in a high output jejuno-cutaneous fistula (Fig. 3). She was supported for the next four weeks with intravenous hyperalimentation with substantial improvement in the skin of her abdomen and reduction in the fistulous drainage. A recurrent episode of candida septicemia necessitated the discontinuance of parenteral hyperalimentation. She was placed on an elemental diet with gradual weight gain and diminution of fistula drainage. Remarkably little residue issued from the fistula which drained most of the gastrointestinal stream. During this period her hemoglobin and serum albumin levels were maintained within normal limits. She was carried on the diet for 12 weeks. When the fistula failed to heal completely she was operated on and found to have a tear in the jejunum which precluded spontaneous closure. She underwent a successful resection of the fistula and an enteroenterostomy. She had an uneventful convalescence and has done well. She was responding satisfactorily to intravenous hyperalimentation but repeated catheter sepsis required termination of that technique. Similar problems occurred in case 10.

Case 6, Small bowel fistula and cachexia: This 68-year-old male was admitted for the first time in February 1972 with sigmoid diverticulitis complicated by perforation and abscess formation. He was treated by drainage of an intraperitoneal abscess and transverse colostomy. He was readmitted in July 1972 with an ileocutaneous fistula secondary to a second intraperitoneal abscess. He had lost a significant amount of weight, was anemic and hypoalbuminemic. He failed to respond to conventional nutritional support and was then placed on an elemental diet beginning at 1200 ml/24h and gradually increasing it to 3000 ml/24h over a one week period. During the following three weeks he gained nine pounds and the fistula output gradually diminished. His serum albumin rose from 1.8 to 2.8 gm/100 ml and his hemoglobin from 10.3 to 11.5 gm/100 ml.

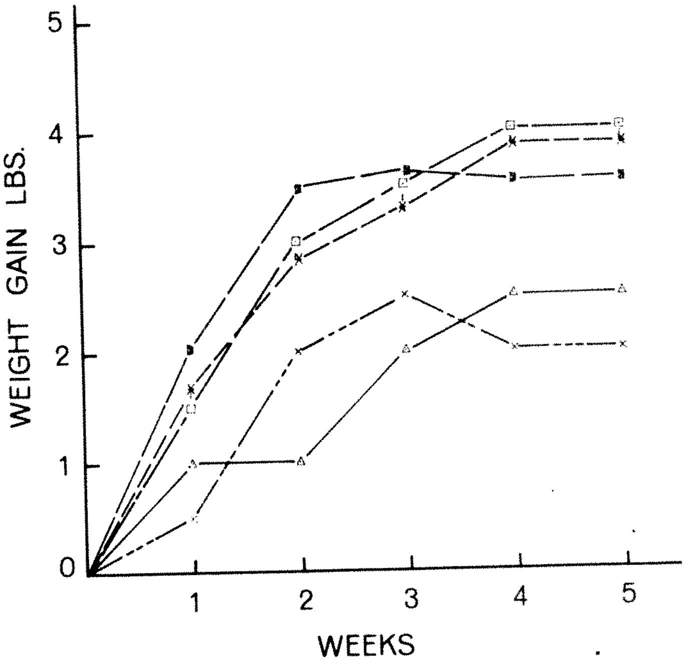

FIG. 1. Pattern of weight gain in lbs in 5 patients on elemental diet.

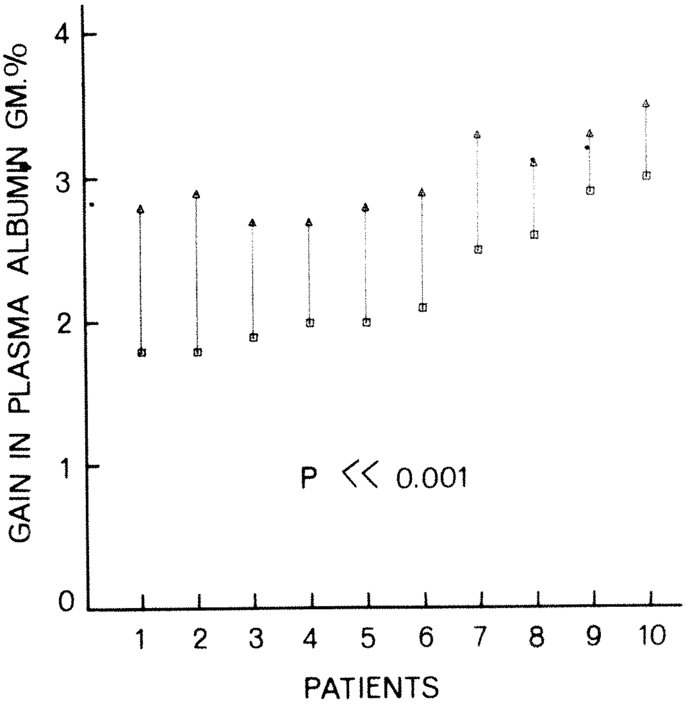

FIG. 2. Serum Albumin levels before and after 3 weeks of elemental diet.

On the 60th day following the start of the elemental diet, he underwent a resection of a small bowel fistula and drainage of an intra-abdominal abscess and was discharged thereafter in good general condition.

This case illustrates the successful use of an elemental diet in a debilitated malnourished patient with sepsis and a small bowel fistula in preparation for surgery. The low bulk of the diet markedly reduced fistula drainage diminishing fluid and electrolyte loss. Similar problems existed in cases 8 and 9.

Case 8, Short bowel syndrome: This 49-year-old female presented a St. Vincent's Hospital in August 1972 with an acute surgical abdomen. Two years earlier she underwent a total abdominal hysterectomy followed by extensive abdominal radiotherapy for an adenocarcinoma of the right ovary at another hospital. Laparotomy revealed a perforation of radiation damaged ileum with a diffuse peritonitis requiring resection of the perforated ileal segment with entero-enterostomy. Postoperatively she developed an enterocutaneous fistula, and an extensive wound infection. This markedly improved on intravenous hyperalimentation. She was discharged with a high output fistula in October 1972, hoping that she might improve further on a regular diet prior to operation. She was readmitted because of inability to maintain her weight by oral alimentation. At this time her weight had dropped from 145 lbs to 116 lbs and her serum albumin was 2.6 mg %. X-ray studies of her gastrointestinal tract demonstrated an enterocutaneous fistula approximately 8 feet from the ligament of Treitz and a jejuno sigmoid fistula approximately one foot further along the small bowel. The remainder of bowel visualized demonstrated radiation damage. It was decided to try an elemental diet beginning at 1200 mg/24h and gradually increasing the diet to 3000 ml/24h. Over the ensuing weeks she has gained thirteen pounds and her serum albumin has increased to 3.1. mg %. She was thought to be ready for resection when a suspicious lesion appeared in the lung. Operation has been delayed. She is working regularly in a responsible position, is on chemotherapy and an elemental diet, and weighs 134 lbs. The main problem is the care of the fistula complicated by some herniation at that site.

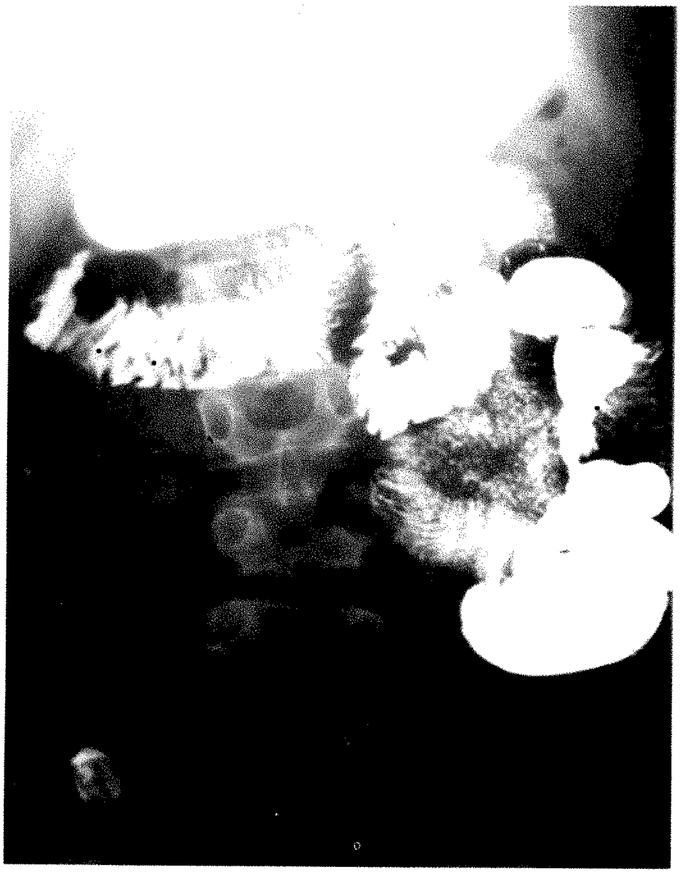

FIG. 3. (Case 9) Upper gastrointestinal and small bowel series in 15-year-old female with regional enteritis and small bowel fistula.

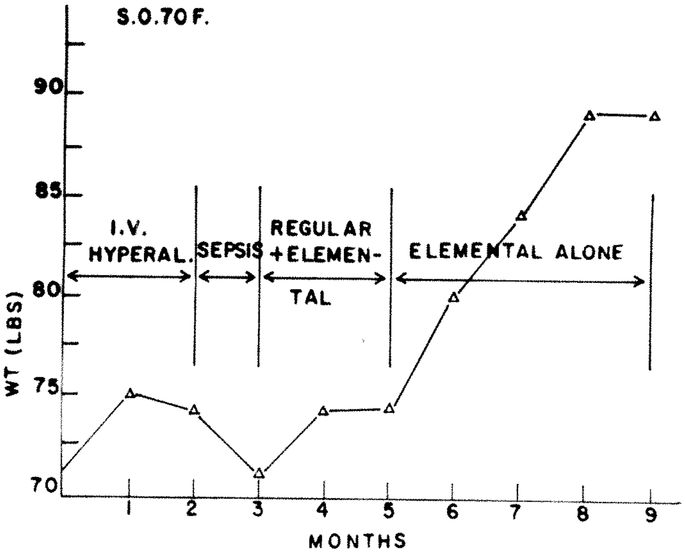

FIG. 4. (Case 10) Seventy-year-old female with esophageal stricture; body weight curve over period of 9 months.

This case demonstrated the beneficial effect of an elemental diet in the treatment of a short bowel enterocutoneous fistula. In addition to a gain in lean tissue and an increase in serum albumin the fistulous drainage rapidly diminished to a point where supplemental intravenous fluids were no longer necessary to maintain adequate fluid and electrolyte balance. The only portion of this patient's gastrointestinal tract which is functioning is the first 8 feet yet her nutritional status at this time is essentially normal after 4 months of elemental nutrition. The short bowel problem also existed in case 9.

Case 10, Esophagogastric obstruction: This 72-year-old female was admitted in February 1971 because of a perforated duodenal ulcer for which she underwent plication of the ulcer. Six months later she underwent a subtotal gastric resection because of intractable ulcer pain. Postoperatively a severe reflux esophagitis secondary to prolonged nasogastric suction, resulted in an esophageal stricture. She was initially supported with parenteral hyperalimentation and received esophageal bouginage with some success. Two episodes of catheter sepsis, the second leading to septic shock necessitated abandonment of intravenous hyperalimentation. The weight gain she sustained during this period was rapidly lost. She was placed on a blenderized diet and an elemental diet was given as a supplement. She failed to gain significant weight on this regime and her serum albumin levels remained unchanged during this interval. She was then placed exclusively on an elemental diet (Fig. 4) beginning at 1200 ml/24h and gradually increasing this to 3000 ml/24h. She gained 16 pounds over the following 12 weeks and her serum albumin rose from 2.0 to 2.8 gm/100 ml and her hemoglobin rose from 10.9 to

11.7 gm/100 ml. Continued bouginage failed to dilate the esophagus sufficiently to allow her to ingest solids. She then underwent a side-to-side esophagogastrostomy without complication.

Recurrent catheter sepsis necessitated discontinuing parenteral hyperalimentation in this case. Although she was able to ingest liquids after bouginage she failed to gain significant amounts of weight on a blenderized diet which caused early satiety. The elemental diet was far more successful as the sole source of nutrition rather than as a supplement.

Discussion

The data presented support the thesis that elemental diets given to patients in catabolic states will place them in positive nitrogen balance. All the patients gained weight and had a rise in plasma albumin over several weeks indicating a positive nitrogen balance. The clinical indications in our series were preoperative situations where there was partial obstruction of the intestinal tract, high enterocutaneous fistulas, or radiation enteritis or inflammatory disease of the bowel with only short segments left. The diet was also useful in patients with multiple trauma who were unable to feed themselves because of maxillo-facial injuries.

The advantage of this regime is the oral intake which is bulk free and virtually fat free. It requires very little digestion and does not require pancreatic or biliary secretions for absorption. It has been used in patients who developed sepsis on intravenous hyperalimentation. The disadvantages are poor taste and sometimes diarrhea related to too rapid administration at the start. Rarely can there be hypertonic dehydration or the dumping syndrome if the diet is given very rapidly. These latter complications were not encountered in this series.

The advantages of placing the intestine at rest and of diminishing secretions has been particularly noticeable in inflammatory and radiation enteritis patients. The patients have been able to absorb the amino acid mixture and go into positive nitrogen balance. These patients have been successfully operated on and the fistulas corrected. The best results have been seen where the elemental diet has been the total oral intake for the patient for several weeks. This requires the cooperation of the patient in this regime.

Addendum

Case 8: Her ileocutaneous fistula was resected in June, 1973. Her ileosigmoid fistula closed spontaneously in July, 1973 and her colocutaneous fistula was resected in November 1973. She is now eating a normal diet after having been on an elemental diet for 14 months.

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Hepatic Cell Adenoma:

A Report of Four Cases

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Four patients with hepatic cell adenoma have been treated at the UCLA Hospital since 1965. The most recent was a 22-year-old woman who underwent subtotal resection of a giant hepatic cell adenoma after an unusual and confusing clinical presentation. The tumor may be the largest reported to date and may have excreted metabolically-active substances. Increased familiarity with the varying clinical and radiographic presentations of these rare tumors may facilitate earlier diagnosis and management.

TRUE HEPATIC CELL ADENOMAS are acknowledged to be the rarest of benign hepatic tumors. Henson *et al.*[6] reviewed the experience with benign hepatic tumors at the Mayo Clinic from 1907 to 1954 and found 76 nonparasitic cysts, 35 hemangiomas, and 13 adenomas, of which only four were hepatic cell type. These measured 15 cm, 10 cm, 6 cm, and 4 cm in largest diameter. Edmondson[4] found only two liver cell adenomas among 418 liver tumors in 50,000 autopsy cases from 1918 to 1954 at the Los Angeles County General Hospital. Berkheiser[2] found one incidental small hepatic cell adenoma in 2,176 cases autopsied between 1949 and 1958 and reported a second one which recurred 6 years after resection. Adam *et al.*[1] listed only four hepatic cell adenomas in a review of liver masses found between 1935 and 1965 at the Memorial Sloan-Kettering Cancer Center. This series contained 106 hemangiomas of the liver. Mercadier and Clot[10] reported 36 hepatic resections, three of which were for hepatic adenomas. Clatworthy *et al.*,[3] however, encountered no adenomas in a review of 75 collected cases of primary liver tumors of children, including 19 of their own. Longmire and Marable[8] described one hepatic cell adenoma resected with long-term survival in a larger series of hepatic resections for a variety of lesions.

Symptoms have been reported to be largely limited to pressure effects of large tumors.[13] Scorer[14] reported on a patient who required emergency left hepatic lobectomy for spontaneous rupture of an hepatic adenoma. Motsay and Gamble[11] recently reported five cases, in two of which symptoms suggested acute cholecystitis; one had jaundice.

Recent experience with a patient who had unusual symptoms of diarrhea, fever, and prostration secondary to an hepatic cell adenoma prompted this report. The excised tumor is among the largest described in the English literature. Three additional cases of true hepatic cell adenomas treated at this institution since 1965 are reported.

Case Reports

Case 1. J.O., a 22-year-old woman, was admitted to the UCLA Hospital after 6 months of diarrhea, bright red rectal bleeding, and lower abdominal cramping pain without weight loss. Ten days before, on admission to another hospital, she was noted to have fever as high as 40 C, malaise, and a strikingly enlarged liver. Hemoglobin value was 10.1 gm %, and white blood cells numbered $5,600/mm^3$. An upper gastrointestinal series showed gastric displacement downward and to the left. Mucosal ulceration of the ascending colon was seen on barium enema (Fig. 1), and an intravenous pyelogram was normal with downward displacement of the right kidney. A liver scan was interpreted as showing 50% replacement of the right lobe by a large mass (Fig. 2). Needle biopsy of the mass was attempted but produced no tissue, and the patient became hypotensive and required 2 units

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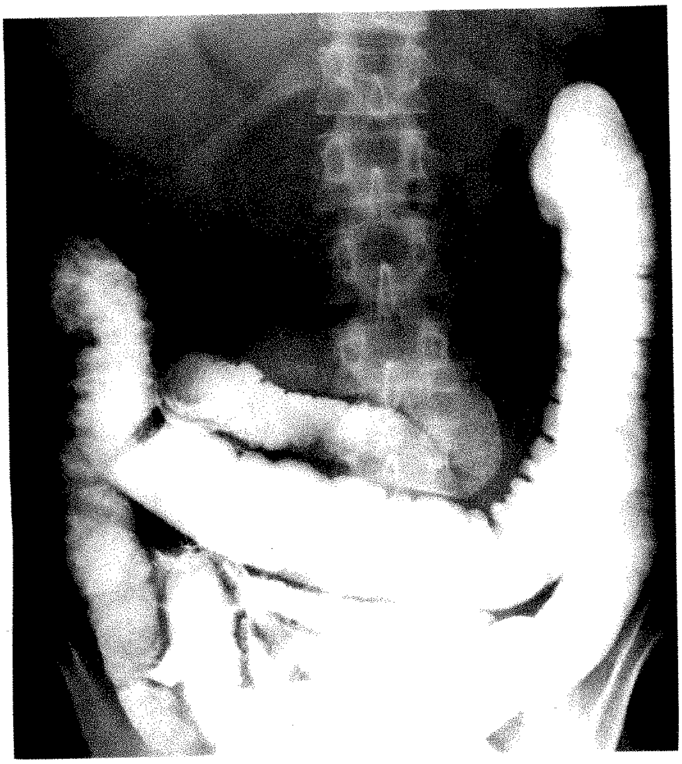

FIG. 1. Barium enema showing the transverse colon displaced downward. Note mucosal ulceration in the hepatic flexure.

of whole blood. An hepatic arteriogram demonstrated an enlarged hepatic artery and moderate hypervascularity in the region of the mass (Fig. 3). Intermittent fever as high as 40.7 C persisted, accompanied by diarrhea (six stools/day), hypokalemia (2.7 mEq/l, and nausea.

She was transferred to UCLA with the diagnoses of primary liver tumor and cholangitis for consideration of hepatic resection.

On admission, the patient's temperature was 41 C, pulse was 124/min, respiratory rate was 32, and central venous pressure was 11 cm (H_2O). She was disoriented and hallucinating. The neck was supple and the chest clear except for a few bilateral dependent rales. The heart was normal with regular tachycardia. A visible bulge was present in the right upper quadrant of the abdomen, but there was no distention and no tenderness. The liver extended 17 cm below the right costal margin to the level of the umbilicus and was non-tender. Collateral venous circulation was noted on the abdominal wall. Bowel sounds were hyperactive. Diarrhea was profuse and although grossly non-bloody, tested 2+ with guaiac reagents. The hematocrit was 30%, and white blood cell count was 3,900/mm^3 with 48% lymphocytes, 36% mature granulocytes, and no bands. Electrolyte determinations showed the following: sodium, 140 mEq/l; potassium, 3.1 mEq/l; carbon dioxide, 14.3 mEq/l; uric acid, 11.0 mg %; calcium, 4.4 mEq/l; total proteins, 5.6 gm %; albumin, 2.4 gm %; alkaline phosphatase, 102 (normal range, 30 to 85); serum glutamic oxaloacetic transaminase, 152; serum glutamic pyruvic transaminase, 33; bilirubin, 1.9 mg % total, 1.5 mg % direct. Alpha-fetoglobulin was negative; amebic complement fixation and hemagglutination inhibition tests were negative; serum 5-hydroxy indoleacetic acid level was 2.9 (normal range, 1.0 to 7.0). Sigmoidoscopy revealed no abnormalities, and wet mounts of the material obtained showed no amoebae. Chest x-ray film was normal. Blood gas analysis showed an arterial PO_2 of 98 mm Hg; base excess was −12, pH was 7.30 mm Hg, PCO_2 was 27 mm Hg, and HCO_3 was 12.7 mEq/l. A working diagnosis of amebic colitis and hepatic abscess was made. She was treated with gentamicin, 7-chlorolincomycin, metronidazole, and chloroquine, together with vigorous administration of intravenous electrolyte solution and colloid.

Within 12 hours she became afebrile, alert, and oriented, although profuse watery diarrhea, hypokalemia, and acidosis persisted. An episode of pulmonary edema prompted digitalization. Multiple stool examination for ova and parasites were negative, as were febrile agglutinins. Cultures of stool, urine, tracheal, aspirate, and blood did not yield significant pathogens.

In view of the abrupt defervescence, a full 10-day course of anti-amebic therapy was instituted (Fig. 4). She remained afebrile for 8 days and was alert and eating well. She then became febrile, oliguric, azotemic, toxic, and obtunded. The oliguria was believed to be pre-renal secondary to underestimation of her diarrhea and responded somewhat to administration of fluids. The toxic course continued despite re-institution of antibiotic therapy, and an hepatic abscess was considered to be the probable cause.

The patient was prepared for emergency operation. At exploration, a massive tumor was found to occupy the entire right lobe which was enlarged to 3½ times normal size. It was judged to be resectable after dissection of the hilum disclosed no invasion of adjacent organs. After ligation of the right hepatic artery and

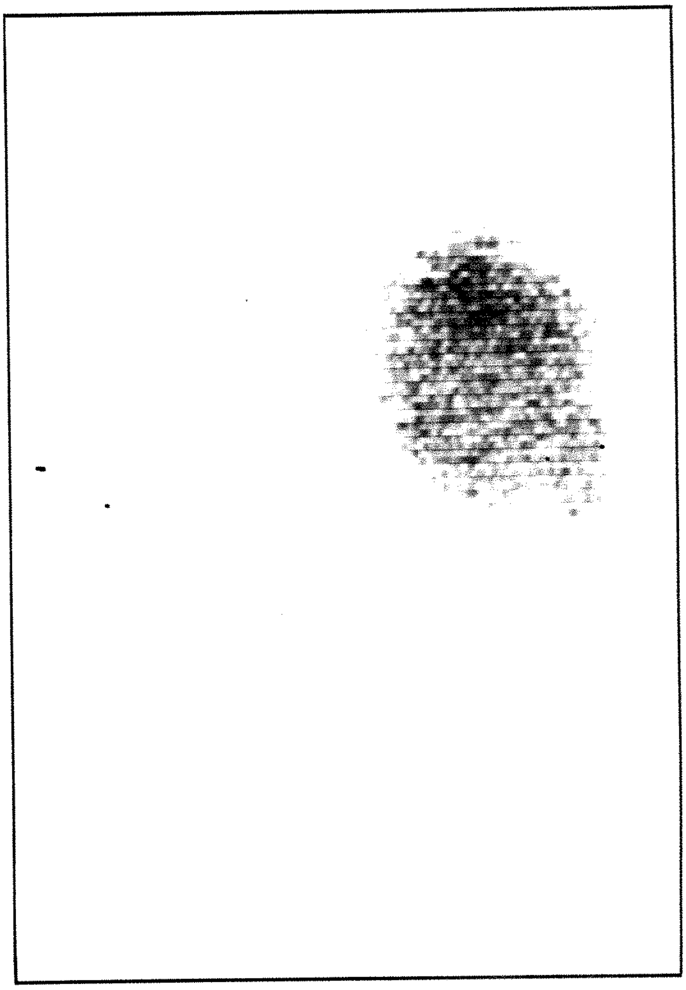

FIG. 2. Hepatic scintiscan showing nonvisualization of right lobe while left lobe shows normal uptake of isotope but is displaced to to the left.

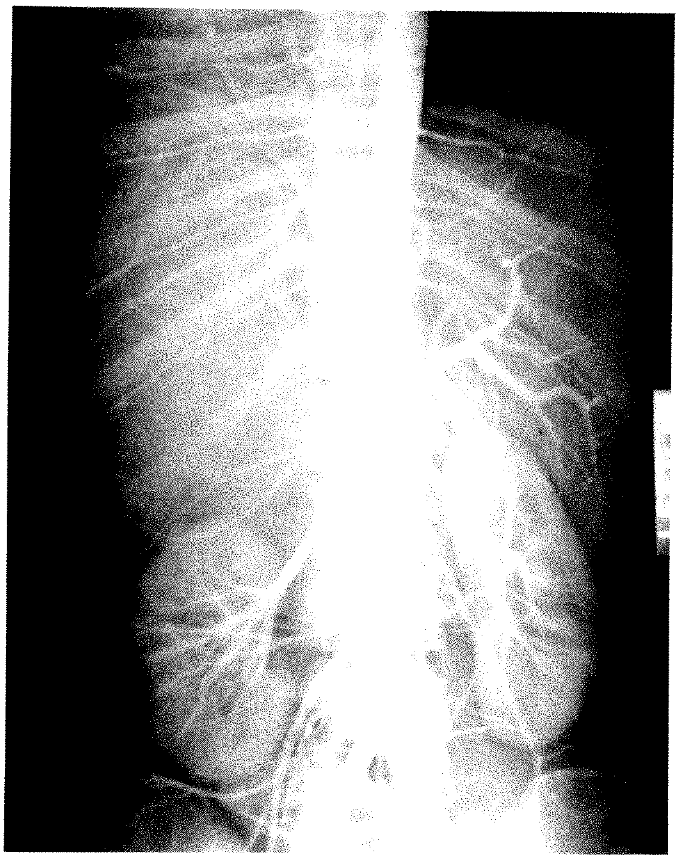

FIG. 3. Aortogram shows large hepatic artery with branches stretched in the greatly enlarged right lobe.

right branch of the portal vein, the large veins on the surface of the tumor continued to pulsate. Extreme vascularity and profuse bleeding were encountered and controlled with application of the Storm-Longmire liver clamp.[15] After the liver was divided slightly to the left of the interlobar plane, it was seen that the central portion of the tumor extended past the resection line into the caudate lobe and medial segment of the left lobe. Further extension of the resection was deemed unwise, and the incision was closed. It was noted that the left lobe of the liver was hypertrophied to two to three times its normal size.

Postoperatively the patient exhibited no serious deficits in liver function (Fig. 5); diarrhea cleared, renal function improved, and fever decreased. On the 19th postoperative day, spiking fevers developed, and on the 21st postoperative day a right subphrenic abscess was drained. She is asymptomatic 15 months after operation. Cultures of the abscess were negative for aerobes and fungi. The resected right hepatic lobe with a portion of the medial segment of the left lobe weighed 3,000 gm and measured 25 × 18 × 12 cm. Pathological examination revealed that the specimen consisted almost entirely of tumor with only a narrow rim of compressed liver tissue surrounding the mass. The tumor was yellow-green in contrast to the surrounding rim of normal red-brown liver. A stellate central fibrous core and central tumor necrosis were present (Fig. 6).

Microscopic examination showed the tumor to be composed of uniform polyhedral cells that resembled mature hepatocytes and were arranged in cords lining delicate sinusoids (Fig. 7). Kupffer's cells were present. No vascular invasion and only rare mitoses were seen. Extensive zones of necrosis and hemorrhage were present centrally, and a pseudo-capsule of compressed fibrotic liver with numerous compressed bile ducts surrounded the adenoma. The surrounding rim of liver was normal.

Case 2. L.W., a 43-year-old woman, had undergone right nephrectomy for hypernephroma about 2 years before exploration

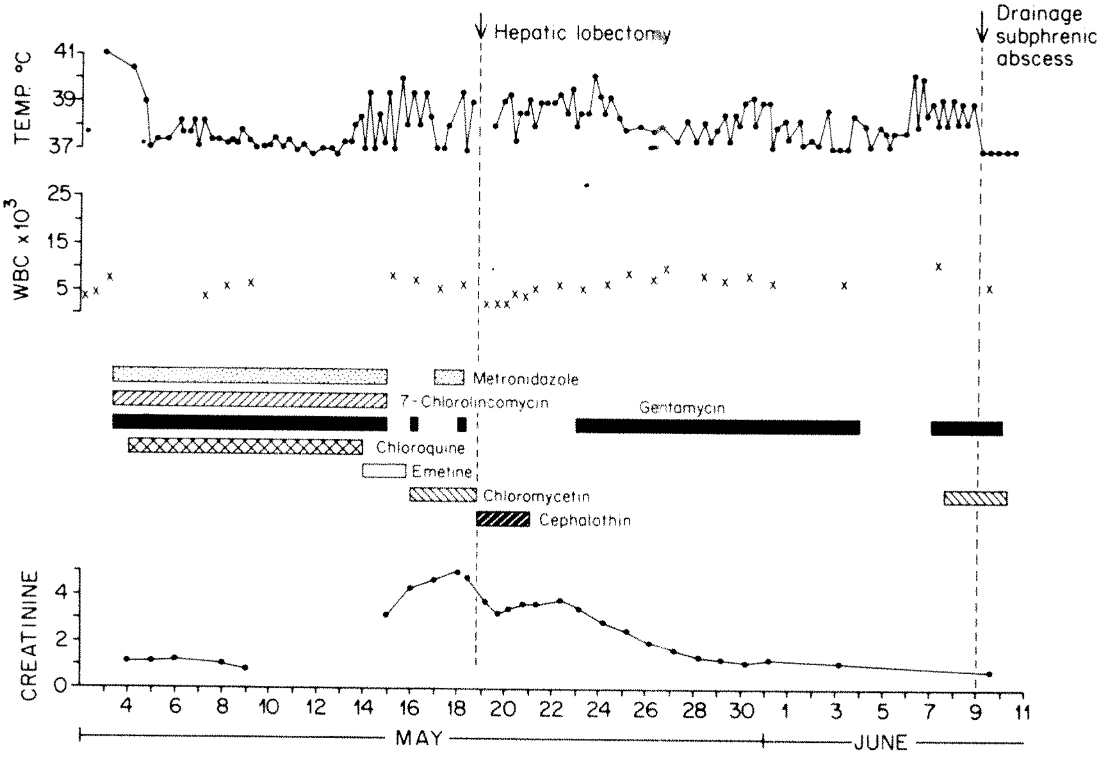

FIG. 4. Graphic representation of the clinical course of Patient #1. Of note is the high fever on admission, prompt response to broad-spectrum therapy, and relapse prior to the first operation.

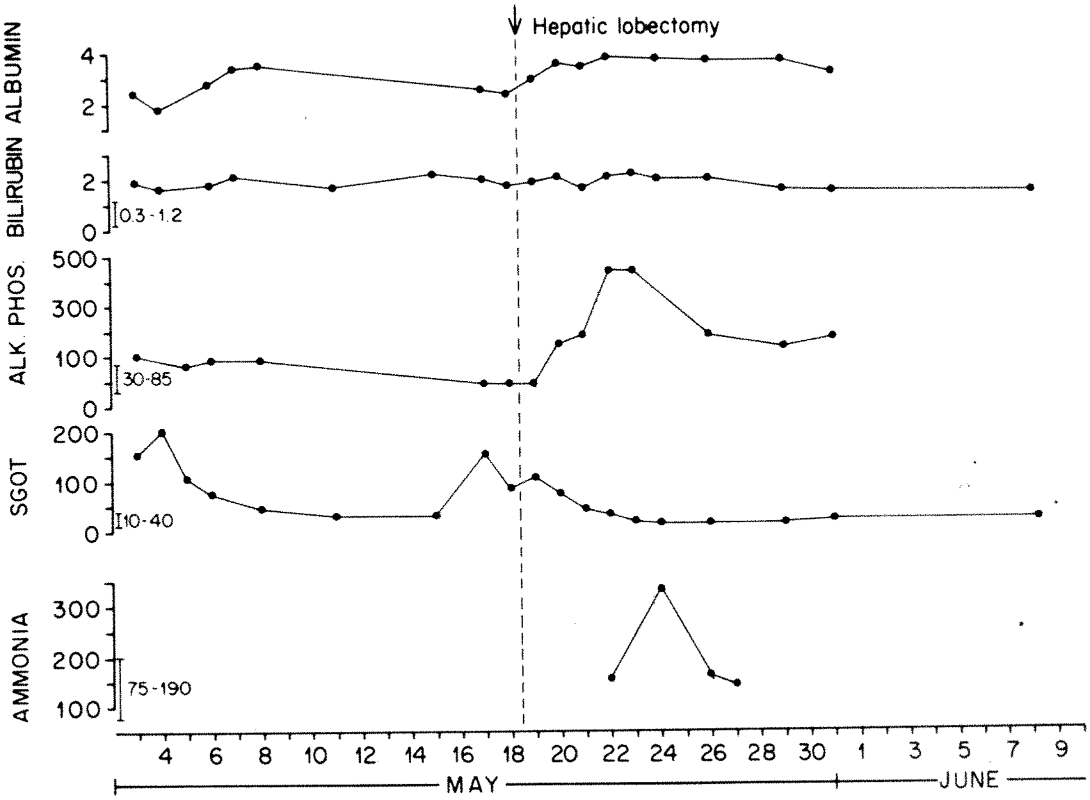

FIG. 5. Liver function parameters during course of illness in Patient #1.

at another hospital for a right upper quadrant mass. A multilobulated cluster of masses was noted in the left lobe of the liver. Wedge excision of one nodule revealed hepatic cell adenoma.

On admission to the UCLA Hospital she denied any symptoms referable to the mass. Liver function tests were normal. Liver scan revealed a defect in the left lobe, and a celiac arteriogram was interpreted as showing no abnormalities. A left lateral hepatic segmentectomy was performed. The specimen contained three nodules, 12 × 12 cm, 1 × 1 cm, and 6 × 6 mm. All were diagnosed pathologically as hepatic cell adenomas.

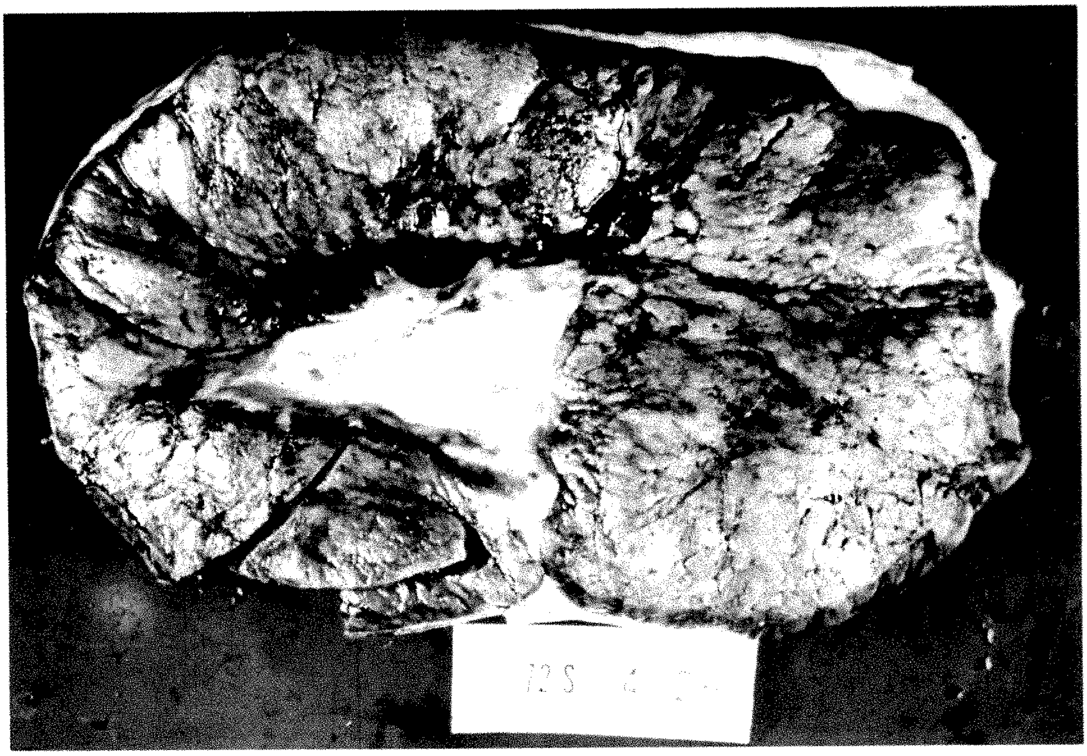

FIG. 6. Specimen of resected right hepatic lobe showing central zone of scar and tumor necrosis. The thin rim of normal hepatic tissue is not visible.

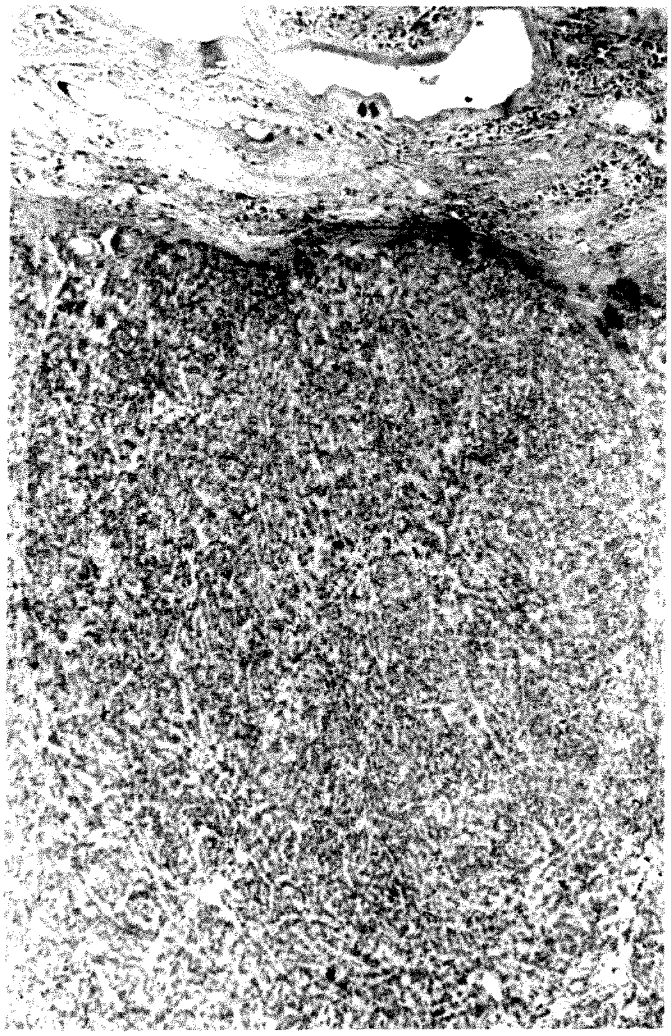

FIG. 7. Histologic section of peripheral zone of hepatic adenoma, low power. The pseudocapsule contains compressed liver tissue, biliary triads, and large venous channels. The tumor consists of mature hepatocytes in cords and sheets, with intracellular bile. There are no bile ducts or biliary triads.

She was symptom-free at time of followup examination 1 year postoperatively.

Case 3. G.E., a 25-year-old woman, was admitted to another hospital with abdominal pain of sudden onset that radiated to her back. There was no history of trauma. At emergency laparotomy a bleeding hepatic tumor was noted, and the patient was transferred immediately to UCLA. On admission blood pressure was 145/110 mm Hg, pulse rate was 116 beats/min., temperature was normal, and hematocrit was 30%. Right hepatic lobectomy disclosed a well-encapsulated 10 × 12 cm orange-yellow tumor with surrounding hemorrhage. Posteriorly, there was found a second 3 cm tumor involving the medial segment of the left lobe. Microscopic examination showed both masses to be composed of normal-appearing hepatic cells in trabeculae. Large venules were seen, but there were no portal zones or bile ducts. No mitoses or atypism was seen.

The patient's postoperative course was satisfactory until the 14th postoperative day when spiking fevers occurred. A sterile pleural effusion developed, but exploration of the right subphrenic space revealed no abscess. Atelectasis of the right lower lobe persisted despite bronchoscopy, and right thoracotomy with resection of the atelectatic right lower lobe was required. She was afebrile when discharged 10 days later. Followup liver scans to 18 months postoperatively showed no change.

Case 4. J.J., a 41-year-old woman, was admitted to another hospital with complaints of post-prandial crampy epigastric pain, fever to 38.3 C, but no nausea or vomiting. At laparotomy, 3 liver masses were noted and biopsied. On admission to UCLA, the initial physical examination was unremarkable. Hematocrit was 43%, white blood cell count was 6,700/mm^3, prothrombin time was greater than 100%, serum glutamic oxaloacetic transaminase was 41, serum glutamic pyruvic transaminase was 39, total bilirubin was 0.6 mg %, alkaline phosphatase was 22 King-Armstrong units/100 ml. An angiogram revealed three vascular masses in both left and right lobes. Review of the original pathology slides showed the lesions to be "compatible with well-differentiated hepatocellular carcinoma or multiple adenomatosis." After cholecystectomy and left and right partial hepatectomy, the pathologic diagnosis was established as "hepatic cell adenoma." Her postoperative course was uneventful. Followup liver scans to 16 months postoperatively were normal.

Discussion

Two of the four patients presented herein had life-threatening clinical problems and required emergency operations. This is in contrast with the majority of previous reports in which operations have been undertaken electively for possible malignancies.[2,5-9,11,13] Although Edmondson[4] has suggested that these tumors may undergo malignant degeneration, particularly in the aged, no documentation of malignancy in any previously biopsied or resected benign adenoma has been found. In Berkheiser's[2] patient, who demonstrated recurrence of a large adenoma 6 years after total removal of an adenoma in the opposite lobe, it was noted that the patient was doing well 8 months after the second operation and that the second tumor was pathologically benign. Malignant potential is difficult, if not impossible, to evaluate in reports published prior to Edmondson's[4] classification of liver tumors in 1958, but as more recent reports accumulate, it appears that malignant change in the true hepatic cell adenoma is unlikely. Thus, the non-malignant but potentially lethal complications that may occur assume greater importance.

Case #1 in this series was characterized initially by colitic symptoms progressive over 6 months, with intractable diarrhea, rectal bleeding, and cramping abdominal pain that progressed to acute toxicity with high fever, severe acidosis, and fluid imbalance. Her critical condition on admission required vigorous therapy. Her prompt defervescence, stabilization of vital signs, and clearing of sensorium were considered at the time to be most compatible with the amebicidal effect of metronidazole. This response, in a patient with ulcerative mucosal lesions on barium enema, toxicity, and an hepatic mass, delayed surgical therapy. Metronidazole has, however, proved to be an effective agent against anaerobic organisms.[12] Considered with the concomitant use of 7-chlorolincomycin and gentamicin, it now seems that tumor infection via the portal circulation from the ulcerative colonic lesions was the basis for her initial clinical condition. Profuse diarrhea persisted, however, until the tumor was resected, then rapidly abated, suggesting that either the products of tumor degeneration or bioactive substances produced by the tumor were the cause of the diarrhea and extremely refractory acidosis. Serum 5-hydroxy indoleacetic acid level was normal the morning after tumor resection, but, unfortunately, the tumor was not properly preserved for detailed biochemical study.

Although the arteriographic findings were considered to be compatible with either primary hepatic neoplasm or amebic liver abscess, the radiologists favored the latter. It is of interest that a similar arteriographic picture is described for the hepatic cell adenoma presented by Palubinskas *et al.*[13]

The patient has been followed for 15 months since operation and is presently active and free of symptoms. Followup liver scans have shown some enlargement of the left lobe.

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Clinical Evaluation of Equine Antithymocyte Globulin in Recipients of Renal Allografts:

Analysis of Survival, Renal Function, Rejection, Histocompatibility, and Complications

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Equine antithymocyte globulin combined with azathioprine and prednisone as immunosuppressive therapy in 50 transplant recipients prolonged allograft survival and seemed to modify the severity of rejection episodes. Although nine patients died from a variety of causes, only three kidneys were lost to rejection, one of which was hyperacute. There were no serious untoward hematologic or systemic effects caused by the ATG, and all patients completed the course of therapy. Infection, a serious and frequent complication of transplant patients, was encountered no more often than in other transplant series not using ALG. The data pertaining to the clinical value of ATG, although suggestive in terms of its immunosuppressive effects, is still not conclusive; and a definitive answer to this question awaits further evaluation in a series of cadaveric recipients in a randomized-double-blind study.

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THE INTRODUCTION of antilymphocyte globulin to clinical renal transplantation by Starzl [22] in 1967 stimulated other transplant centers to develop a variety of antilymphoid preparations which were combined with azathioprine and prednisone as immunosuppressive therapy for patients receiving renal allografts. In spite of strong experimental evidence supporting the immunosuppressive properties of antilymphocyte sera in prolonging skin allografts in rats,[29] mice[10] and in canine renal allografts,[13,18,23] the results from clinical trials regarding its immunosuppressive value are less conclusive. Evaluating the results of patients receiving renal transplants treated with antilymphocyte globulin in conjunction with azathioprine and prednisone is complicated by the many types of antilymphocyte sera preparations. The source of antigenic material has included lymphocytes from spleen,[23] thoracic duct,[27] thymus,[6,11] lymph nodes,[14] and lymphoblasts [17] from cell culture. Another factor in the preparation involves the host animal used to prepare the antisera. The horse,[9,14,17,22] goat [19] and rabbit [11] have all been used with varying immunization schedules.[12] The antisera (either crude globulin or the 7-S fraction) has been administered in dosage concentrations from 2–4 mg/kg/day to more than 20 mg/kg/day by either the intramuscular or intravenous route. The difficulty in assessing the immunosuppressive value of these products is enhanced when one considers the many variables encountered in the transplant patient. These include the histocompatibility differences between the donor and the recipient, the use of cadaver organs with various methods of preservation and the previous sensitization of recipients to antigens, some of which may not be detected by present methods of histocompatibility testing.

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This study was initiated with the above difficulties in mind in an effort to determine the adjunctive value of equine antithymocyte globulin administered with prednisone and azathioprine to patients receiving allografts from living-related donors and cadavers. The results are analyzed according to patient survival, renal function, histocompatibility and the complications encountered, including rejection and infection.

Clinical Material and Methods

Patients

Forty-nine patients received 50 renal transplants between December of 1968, and December of 1971. The study period terminated December 1, 1972 with all living patients followed from 12 to 47 months. Thirty-nine patients obtained kidneys from related-living donors (RLD) with one patient receiving a second transplant. Eleven patients received cadaveric kidneys (CD) (See Table 1). Antithymocyte globulin (ATG) was administered to consecutive patients except for two patients when the supply was unavailable. Those patients were deleted from the study. Thirty-six patients were male and 13 female with an age distribution from 11 to 51 years (See Table 2). Chronic glomerulonephritis was the primary disease in 31 patients, chronic pyelonephritis in 12 patients and arteriolonephrosclerosis in three patients. Two patients had polycystic kidney disease, and one had congenital hypoplasia (Table 3).

Thirty-one of the 40 living patients had renal biopsy specimens taken from functioning kidneys at various intervals in the post-transplant course. All were examined by light microscopy and selected specimens studied by electron microscopy and immunofluorescent technique. Autopsies were performed on six of the nine patients who died, and two others had either a renal biopsy or transplant nephrectomy. Only one of the deceased patients did not have renal tissue for histologic evaluation. Nine patients, living and well with a serum creatinine of less than 2.0 and stable renal function, also did not have renal biopsies.

Transplant Procedure

All patients but one were prepared for transplantation by hemodialysis. The single exception was an 11-year-old boy with bilateral renal hypoplasia. Two patients retained their kidneys, and the remaining patients were nephrectomized prior to transplantation. The kidney was placed in the pelvis by the extraperitoneal approach utilizing the iliac vessels for reconstruction in every instance except one where the kidney was positioned within the abdominal cavity. A ureteroneocystostomy was performed in all patients.

TABLE 1. *Clinical Material*

Total Number of Transplants*	50
Total Number of Patients	49
Recipients of Related Donors (RLD)—39	
Parents	18
Siblings	21
Offspring	1
Recipients of Cadaveric Donors (CD)—11	
Total Number of Patients Alive	40
Total Number of Patients Dead	9

* One patient received a second transplant.

TABLE 2. *Age of Patients at Transplant*

10–19	05
20–29	17
30–39	13
40–49	14
over 50	01
Total	50

Tissue Typing

Histocompatibility matching, performed by a modification of the cytotoxicity technique of Terasaki, was completed prospectively in all donor and recipient patients. The antigen profile was tested with antisera as well as screening for humoral antibodies in the recipient patient by the lymphocytotoxicity crossmatch.

Preparation and Immunosuppressive Activity

Horse antihuman thymocyte globulin (ATG) was prepared by injecting a suspension of 1×10^9 to 1×10^{10} human thymocytes into horses with 90% viability as determined by trypan blue. The first injection of thymocytes, combined with equal volumes of Freund's adjuvant was administered by the intramuscular route. A second and third injection of a similar number of thymocytes, suspended in saline, were given intravenously 21 and 28 days later. The horse was bled on day 35 and then allowed four weeks to recover before the final intravenous injection of thymocyte suspension. The second phlebotomy was performed seven days later with no horse receiving no more than two bleedings. The antithymocyte serum (ATS) was separated from the red cells and decomplemented at 56 C for 30 minutes. The hemagglutinin antibody was removed by two absorptions with human red cell stroma, and the globulin fraction prepared by ammonium sulfate precipitation (45%). The initial leukoagglutinin titer of 1:59,000 in the ATS was usually reduced to a titer between 1:2,000 and

TABLE 3. *Pathology*

Chronic Glomerulonephritis	31
Chronic Pyelonephritis	12
Arteriolonephrosclerosis	03
Polycystic Disease	02
Congenital Hypoplasia	01
Total No. Patients	49

P, 24, 777

1:20,000 after absorption with red cell stroma. The final hemagglutinin titer of all ATG prior to use was less than 1:32. Sterilization was achieved by high energy irradiation (performed by Dr. Kenneth Wright of the Massachusetts Institute of Technology, Boston). The immunosuppressive effect of ATG was tested in four Rhesus monkeys receiving skin allografts. The animals were treated with ATG, 2 mg/kg/day intramuscularly for 21 days (seven days before the skin graft and 14 days afterwards). This dosage schedule prolonged skin allografts in all animals with 80 to 90% viability of the skin for more than 21 days. The grafts sloughed four to nine days after discontinuing the ATG.

Immunosuppressive Management

All renal allograft recipients received azathioprine, prednisone and intramuscular ATG (2–4 mg/kg/day) as immunosuppressive therapy. Antithymocyte globulin was administered to patients receiving kidneys from related donors for seven days prior to transplantation and for 14 days post-transplantation for a total of 21 injections. Cadaveric recipients were given ATG by the same route for 28 days starting on the day of surgery. All patients were skin tested with horse serum to exclude individuals sensitive to the serum. Recipients of related-living donor kidneys were pretreated with azathioprine two days before transplantation (3 mg/kg/day) and continued post-transplantation with gradual reduction of the azathioprine to 1 to 2 mg/kg/day depending on the white blood cell count. Prednisone, 4 to 5 mg/kg/day started on the day of transplantation, was gradually reduced to 30 mg/day one month post-transplantation in patients receiving kidneys from related-living donors and to 40 mg/day in cadaveric recipients.

Acute rejection was defined as an increase in the BUN 10 mg/100 ml and in the serum creatinine 0.5 mg/100 ml above the previous stable level of renal function without evidence of ureteral obstruction. The usual clinical criteria of weight gain, hypertension, fever and increase in kidney size with tenderness were additional factors contributing to the diagnosis of rejection. Treatment of acute rejection included an increase in oral prednisone to 4–5 mg/kg/day with gradual reduction combined, on occasion, with intravenous methylprednisolone. Allograft irradiation, totaling 600 r to the midplane of the kidney, was given in 4 divided doses of 150 reach.

Results

Surviving Patients and Renal Function

Forty of the 49 patients receiving 50 renal transplants are alive from 12 to 47 months after surgery with an average followup of 24 months (See Table 4). Thirty-one of these patients received kidneys from related donors, and nine obtained kidneys from cadaveric origin. The surviving patients with functioning allografts were divided into three groups (Table 5): Group I—twenty-five patients with a serum creatinine of 1.5 mg/100 ml or less (RLD-18, CD-7); Group II—twelve patients with a serum creatinine between 1.6 and 2.0 mg/100 ml (RLD-10, CD-2) and Group III—three patients with a serum creatinine between 2.1 and 4.0 mg/100 ml (RLD-3). Five of the 40 patients with functioning allografts have evidence of chronic rejection (RLD-4, CD-1) characterized by decreasing renal function, proteinuria and histologic confirmation by biopsy.

Tissue Typing data was correlated with the status of renal function (Table 5). All seven patients considered to be HLA identical (A Match) maintained a serum creatinine of 1.5 mg/100 ml or less even though three of the seven had mild or moderate rejection episodes easily reversed with Prednisone. Seven of the eight patients with a B Match maintained excellent renal function and are also in Group I. The other B-Match patient is in Group II. It is significant to note that six of 16 patients with a D Match are also classified in Group I, indicating that two or more antigen mismatches may still be compatible with excellent renal function. Haplotype analyses were performed on 30 donor/recipient combinations with similar results to the phenotypic analysis. Again, patients with identical haplotype analysis maintained excellent renal function (Group I), whereas recipients with two haplotype differences have suboptimal renal function, some with evidence of chronic allograft rejection (Group II and III). Only one patient underwent hyperacute rejection; retrospective analysis indicated previous sensitization in this instance.

Patient Deaths and Transplant Failures

There were nine deaths and one transplant failure secondary to chronic rejection requiring retransplantation (Table 6). One patient (TX 11) sustained a hyperacute rejection, was returned to dialysis and died 11 months later following a nearly total small bowel resection for volvulus with gangrene. Three patients (TX 12, 19 and 20) died of myocardial infarction with severe coronary artery disease, 24, 16 and 3 months respectively after transplantation. One patient with chronic rejection (TX 10) died of septicemia at 18 months. Two patients (TX 41 and 54) died of cytomegalovirus with hepatic failure (one with normal renal function and one two months after transplant nephrectomy for rejection of a cadaveric kidney). One patient (TX 18) died of a pulmonary embolus following a gastric resection for a bleeding marginal ulcer six months after transplantation. Six of the nine patients

TABLE 4. *Analysis of Forty Patients with Functioning Kidneys*

TX. No.	Age	Donor	Tissue Typing	Duration of Function (mos)	BUN	CR	CRCL	24-hour Protein mg%	Azathioprine	Prednisone	Anti-Hypertensive
6	34	P	D	47	25	1.8	60	450	100	12.5	no
7	45	P	D	45	36	1.8	30	652	100	15	no
8	33	S	B	44	23	1.3	114	450	150	5	yes
9	50	S	B	44	14	0.7	102	470	150	5	yes
15	31	P	C	38	27	1.4	79	255	150	10	no
16	30	S	B	37	15	1.4	110	480	150	10	yes
17	22	P	D	37	38	2.2	45	770	100	10	yes
21	23	S	A	32	15	0.9	84	240	100	10	no
22	32	S	A	32	20	1.1	113	211	100	10	no
23	11	P	D	29	18	0.9	72	608	100	7.5	no
24	24	S	A	29	25	1.4	92	400	150	15	yes
26	45	Cd	C	29	17	1.0	124	353	75	15	yes
27	38	Cd	C	29	17	1.0	118	945	100	15	no
28	40	Cd	C	24	25	0.9	83	306	75	15	yes
29	27	P	C	24	27	1.5	92	784	150	12.5	no
30	25	P	D	24	36	2.2	34	207	100	25	no
31	33	Cd	D	24	22	1.0	56	1700	75	20	no
32	23	S	D	22	27	1.8	72	415	200	15	yes
33	23	P	D	21	23	1.4	78	250	75	10	no
34	38	Cd	B	21	21	1.1	123	200	100	20	no
35	39	Cd	D	21	27	1.3	147	129	100	20	yes
36	14	P	C	19	28	1.7	49	620	125	15	yes
37	24	Cd	D	19	24	2.0	107	552	150	25	yes
38	42	O	B	18	20	1.0	72	275	100	15	no
39	26	S	D	17	37	3.5	35	675	150	20	yes
40	42	Cd	D	17	27	1.0	77	120	150	17.5	yes
42	36	S	C	17	32	1.9	59	382	125	15	no
43	20	P	C	17	27	1.7	61	1793	150	15	yes
44	24	S	A	17	15	1.1	111	240	150	15	no
45	40	S	A	16	17	1.3	88	600	125	12.5	no
46	43	S	B	16	18	0.9	118	128	150	15	yes
47	26	S	B	15	13	1.2	97	450	125	15	no
48	25	S	B	14	24	1.9	58	257	150	15	yes
49	33	P	D	14	38	2.0	45	232	100	15	no
50	34	P	C	13	40	1.7	50	696	100	15	yes
51	24	S	A	13	17	1.2	122	100	150	15	no
52	17	P	C	13	23	1.0	74	202	125	17.5	no
53	27	P	D	13	39	1.7	60	1278	100	17.5	yes
55	20	Cd	D	12	41	1.6	98	936	175	25	yes
56	46	S	A	12	28	1.0	76	1543	150	17.5	no

who died were over the age of 40, and two were less than 20 years of age.

Pathologic Examination of Renal Allograft Tissue

Although renal biopsy specimens were obtained frequently during episodes or acute rejection, the histologic appearance seldom correlated with renal function except in Transplant 54 where cortical necrosis was present and necessitated transplant nephrectomy several days later. Renal tissue from patients in Group I (17 of 25, Table 5) showed the least amount of vascular injury and intestinal fibrosis on microscopic examination. The degree of mononuclear cell infiltration varied from patient to patient and at times appeared more prevalent than expected from the excellent renal function (Fig 1).

Complications

Rejection. There were 44 acute rejection episodes in 32 patients (Table 7). Twenty-eight rejections occurred in the first 60 days and 31 within 90 days after transplantation. Thirteen late rejection episodes developed after the third post-transplant month, nine of which were diagnosed after six months. These late rejections were

TABLE 5. *Comparison of Renal Function and Tissue Typing in Forty Living Patients*

Group	No. Pts.	Renal Function Cr	Source of Kidney		Typing*			
			RLD	CD	A	B	C	D
I	25	1.5 or less	18		7	6	2	3
				7	0	1	3	3
II	12	1.6–2.0	10		0	1	4	5
				2	0	0	0	2
III	3	2.1–4.0	3		0	0	0	3
				0	0	0	0	0
Total	40		31	9	7	8	9	16

* A—Identical.
B—No group mismatch.
C—1 group mismatch.
D—2 or more group mismatches.

TABLE 6. *Analysis of Ten Patients with Transplant Failure or Death*

TX. No.	Age	Donor	Tissue Typing	No. Rejections	Duration of Function	BUN (at death)	CR (at death)	Azathioprine	Prednisone	Dead	Autopsy	Comments
5	23	P	D	2	24					no		Chronic Rejection Retransplant
10	14	P	C	1	18	105	4.1	75	17.5	yes	yes	Septicemia
11	48	S	C	1	0	Tx. Nephrectomy				yes	yes	Postoperative Intestinal Obstruction
12	43	S	C	1	24	14	1.0	150	17.5	yes	no	Myocardial Infarction
18	41	S	B	1	6	23	0.9	150	32.5	yes	yes	Pulmonary Embolus
19	42	S	D	1	3	29	2.7	100	30	yes	yes	Myocardial Infarction
20	39	CD	C	2	16	105	6.0	100	25	yes	yes	Myocardial Infarction
25	19	P	D	0	16	34	1.1	100	17.5	yes	no	Pneumonia (Pneumocystis)
41	48	S	B	1	10	26	1.3	100	25	yes	yes	Hepatitis (Cytomegalovirus)
54	45	CD	D	2	2	Tx. Nephrectomy				yes	no	Liver Failure, Pneumonia (Cytomegalovirus) 4 mos. P Tx.

often associated with prednisone reduction and easily reversed after increasing the steroid dosage. The post-transplant immunologic course was categorized into five types (Table 8): Type 0—no rejection (18 patients); Type 1—a rejection episode where the BUN remained less than 40 mg/100 ml and the creatinine less than 2 mg/100 ml (12 patients); Type 2—a rejection episode where the BUN increased to more than 40 mg/100 ml and the creatinine above 2 mg/100 ml (15 patients); Type 3—a rejection episode similar to Type 1 or 2 but with deranged renal function for more than 30 days (1 patient); Type 4—reversible rejection requiring dialysis (1 patient); Type 5—irreversible rejection, acute, hyperacute or chronic (3 patients). Thirty-nine of the 44 rejections were classified as Type 1 or Type 2. A single rejection crisis occurred in 23 patients. Two rejection crises developed in six patients, and three patients had three rejection episodes each. Thirteen of the 25 patients with excellent renal function (Group I, Table 5) had single rejection episodes all readily reversed with prednisone occasionally combined with x-ray therapy. Seven of the 12 patients with good renal function (Group II, Table 5) had one episode of allograft rejection, reversed with some difficulty. Five patients had two such crises requiring substantial steroid therapy and x-ray therapy. All three patients with fair renal function had two or three rejection episodes with subsequent unstable renal function requiring increased prednisone dosage for control (Group III, Table 5). One patient (TX 32) sustained acute rejection on the seventh post-transplant day and required two dialyses until renal function resumed. He is now 22 months post-transplantation with a creatinine of 1.8 mg/100 ml. Eighteen patients (RLD-12, CD-6) never experienced a rejection episode. Eight were a C or D Match (parent to offspring), six an A or B Match (sibling) and four received cadaveric kidneys (2-C Match, 2-D Match).

Infections. Eleven patients sustained an infection in the *early* (less than six weeks) post-transplant period (Table 9). In five patients, the process involved the surgical wound, two with perinephric extension. All of these patients recovered. Sixteen patients developed serious infections more than six weeks after transplantation, and three died. Ten of these late infections followed augmented immunosuppressive therapy for rejection. Gram-negative bacilli, the most common bacteria isolated, were the responsible organisms in 16 instances (Table 10). There were four patients who developed serious viral infections, and one died. Although all four patients with fungal infections recovered, the three patients with Pneumocystis carinii expired from pulmonary insufficiency (Table 10).

Malignancy. Four patients developed malignant tumors; three squamous cell carcinoma of the skin and one systemic Hodgkin's Disease. All tumors occurred two years or more after transplantation. Local excision was adequate treatment in the squamous cell tumors and chemotherapy was given in the patient with Hodgkin's Disease.

Skeletal Complications. Eighteen patients had skeletal complications, 14 of whom developed aseptic necrosis of the femoral head. Nine of these individuals required replacement with an Austin-Moore prosthesis and made a complete recovery. Three patients fell, sustaining intertrochanteric fractures, and one spontaneously fractured a pelvic ramus. Overt hyperparathyroidism could not be

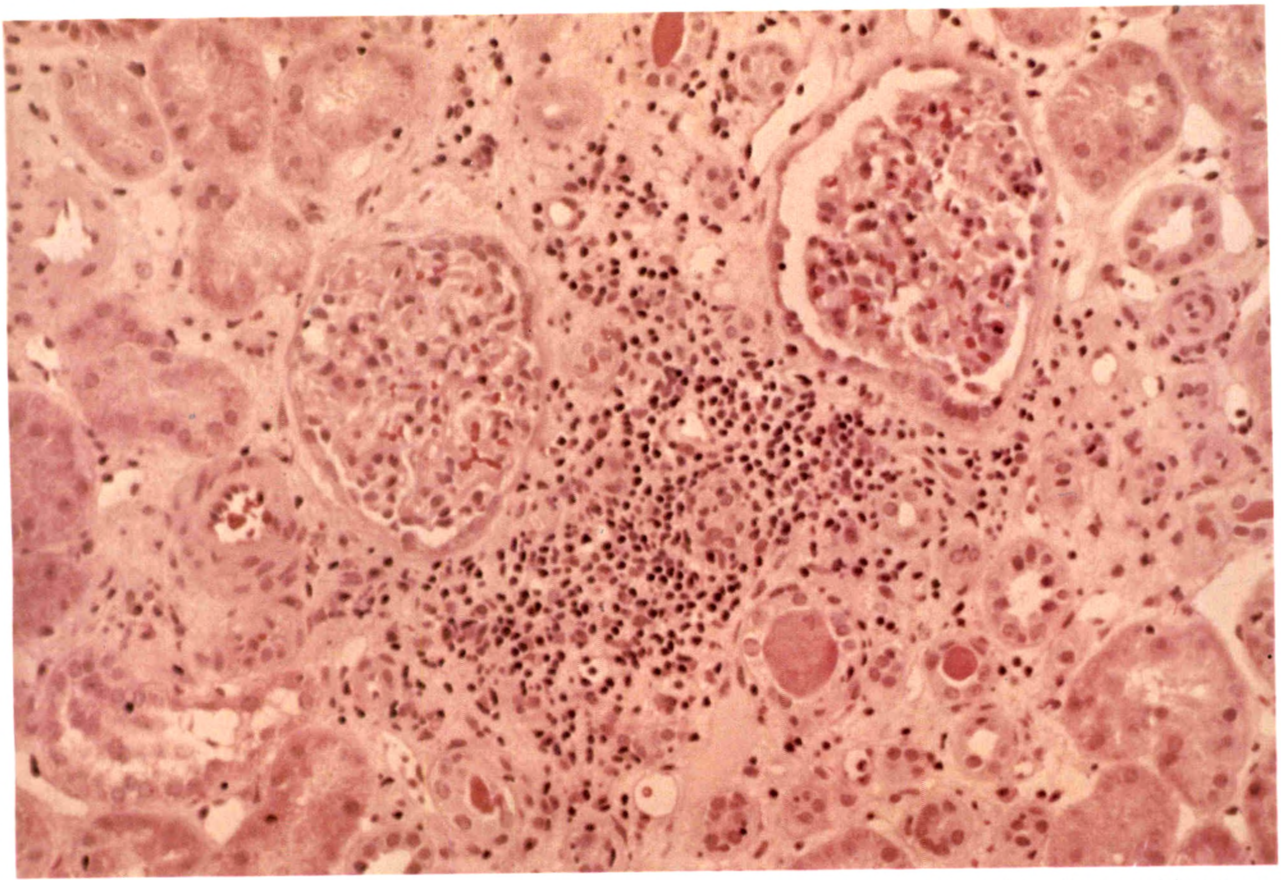

FIG. 1. A renal biopsy of Tx. 26, 29 months post cadaveric transplantation. The patient has maintained excellent renal function without rejection since transplantation in spite of the mononuclear cell infiltrate noted in this specimen.

implicated as a factor in these patients, and there was no definite correlation between the total steroid dosage and the development of aseptic necrosis (Table 9).

Urologic Complications. Five patients developed urologic complications including ureteral necrosis, ureteral perforation and vesico-cutaneous fistulae. None were fatal, and all patients recovered. Two patients with lymphoceles developed ureteral obstruction and hydronephrosis; both were cured after drainage.

Gastrointestinal Complications. Four patients had gastrointestinal complications; two with small intestinal obstruction secondary to adhesions, and one each with gastroduodenal and marginal ulceration with bleeding.

Psychiatric Complications. Two patients required hospitalization for two and four months for psychiatric problems. Both of these individuals recovered, and in neither could steroids be implicated as a causative factor.

Reactions to ATG. Erythema, induration and pain at the injection site were common reactions in all patients receiving ATG. Fever and leukocytosis were almost al-

TABLE 7. *Rejection Crises in 32 Patients*

Interval from Transplantation	No. of Crises
1–7 Days	1
8–30 Days	14
31–60 Days	13
61–90 Days	3
91–180 Days	4
181–365 Days	7
1–2 Years	1
3 Years	1
Total	44

TABLE 8. *Rejection Crises:* Effect upon Renal Function

Type*	No. Patients	No. Rejections
0	18	0
1	12	12
2	15	27
3	1	1
4	1	1
5	3	3

* Type 0—No evidence of rejection.
Type 1—BUN < 40; Cr < 2.0.
Type 2—BUN > 40; Cr > 2.0.
Type 3—As in 1 or 2 but with deranged function for more than 30 days.
Type 4—Reversible but requires dialysis.
Type 5—Irreversible rejection.
12 patients had more than one rejection episode.

TABLE 9. *Complications Excluding Rejection*

Type			No. Patients
Infection			27
	Bacterial	17	
	Viral	5	
	Fungal	3	
	Protozoan	2	
Skeletal			18
	Aseptic necrosis	14	
	Intertrochanteric fracture	3	
	Pelvic ramus fracture	1	
Urologic			5
Gastrointestinal			4
	Intestinal obstruction	2	
	Gastroduodenal ulceration with bleeding	2	
Psychiatric			2
Lymphocele			2

A number of patients had two or more complications.

ways present and seemed to decrease after the first seven days. There were no anaphylactoid reactions in the 1,207 injections of ATG. Lymphopenia was consistently observed three to five days after the onset of the administration of the ATG and persisted in most instances until the ATG was discontinued. The hematocrit remained stable, and there was no evidence of thrombocytopenia. Lymph nodes adjacent to the iliac vein were biopsied during transplantation and consistently showed paracortical depletion.

Discussion

The critical question relating to the clinical value of equine ATG as an immunosuppressive agent prepared and administered to this series of 50 renal allograft recipients in conjunction with azathioprine and prednisone is difficult to answer. However, certain parameters can be examined in the clinical analysis of these transplant recipients. These include: 1) the quality and duration of renal function correlating these results with the histocompatibility differences between the donor and recipient, 2) the number and severity of rejection episodes, and 3) the frequency and type of infectious complications in the post-transplant course.

TABLE 10. *Microorganisms Causing Disease in Patients After Transplantation*

Organism	No. of Infections
Bacteria	
Diplococcus pneumoniae	2
Staphylococcus aureus	4
Escherichia coli	3
Pseudomonas	3
Other gram negative bacilli	10
Fungus	
Cryptococcus	3
Nocardia	1
Viruses	
Herpes virus hominis	2
Cytomegalovirus	2
Protozoa	
Pneumocystis carinii	3

Since the effects of antigenic disparity between donor and recipient patients can be modified by immunosuppressive agents, the prolonged survival of allografts reflects the efficacy of the immunosuppressive regimen. In this series 40 of 50 patients (80%) have functioning kidneys 12 to 47 months later. More important, only three patients (6%) lost their kidneys as a result of rejection. The remaining seven patients (14%) died with functioning kidneys, four of whom had normal renal function at death. The quality of renal function is encouraging in that 37 of the 40 patients (92%) with functioning kidneys (average 24 months) have a serum creatinine less than 2.0 mg%. If the A and B-matched patients are excluded from the analysis, 22 of 25 patients (eight CD and 14 RLD) have a serum creatinine less than 2.0 (88%). This group of patients represents those with the greatest degree of antigenic disparity.

Allograft rejection was noted 44 times in 32 patients; 18 patients were free from episodes of rejection. Only one patient (TX 54) developed irreversible acute fulminating rejection. Twelve of the rejections were classified as Type 1 (Table 8), and their rejections were easily reversed. This data supports the observation of others[11,15] in that ALG appears to modify the severity of acute rejection. The interval of the rejection crises from time of transplantation did not seem to differ from that noted in other transplant reports.

Infection either at the site of surgery or systemically results in part from the effects of immunosuppressive therapy upon the host defense mechanisms and has been noted in transplant patients receiving various anti-rejection protocols.[1,21] A prospective study of infection complicating renal transplantation has been previously reported from this center.[8] This report emphasized two patterns of post-transplantation infection. One occurred "early" and was associated with compromised anatomic barriers and the pretransplantation presence of *Staphylococcus aureus*. The other variety occurred "late," often following treatment for rejection and associated with significant abnormalities in humoral and cellular immunity. The findings of the present study confirm and amplify these conclusions. In particular, *early* infection has been much less common in the more recent patients, presumably because of greater experience with the procedures and the routine use of antistaphylococcal prophylaxis. Late infection occurring in proximity to augmentation of immunosuppressive therapy has continued to occur but in fewer patients. A recent report by Anderson *et al.*[1] has elevated risk factors in transplanted patients and noted that the recent decline in infectious death at their center has been due to: 1) the accumulation of extensive experience with infection; and 2) a decrease in the use of high dose prednisone therapy associated with the introduction of antilymphocyte globulin. It has been our impression that the prednisone "sparing effect" of antilymphocyte globulin has decreased the incidence of late infection.

The untoward effects of the ATG, limited to pain, erythema and induration at the site of injection and fever, were similar to those observed previously.[22] In no instance was an anaphylactoid response observed, and all patients completed their course of treatment. The effect of antithymocyte globulin contaminated with antiglomerular basement membrane antibodies upon the glomerular basement membrane of the renal allograft was reported by Thiel.[26] He noted deposition of anti-GBM antibodies by immunofluorescent technique although light and electron microscopy gave no evidence of glomerulonephritis, and the histologic appearance was indistinguishable from transplant glomerulopathy in recipients not treated with ALG. Busch *et al.*[3] observed that horse IgG was present on renal tissue from two patients receiving equine ALG prepared against thoracic duct lymphocytes. One of these two patients developed nephritis possibly secondary to glomerular basement membrane antibody. Additional support regarding this complication has been presented by Chase *et al.*,[4] who demonstrated ultrastructural changes in kidneys of monkeys receiving intramuscular injections of human antithymocyte globulin. Wilson *et al.*[28] reported that lymphocytes from whole organs, i.e. thymus, spleen and lymph node, produced antilymphocyte sera containing glomerular basement membrane antibodies, whereas sera prepared against thoracic duct cells or cultured lymphoblasts did not. A complete immunoflourescent study has not been completed in this series; and therefore, the question of whether or not equine ATG is deposited with regularity upon the glomerular basement membrane remains to be determined. However, examination of renal biopsy material by light microscopy on 17 of 25 patients with excellent renal function (Group I, Table 5) did not reveal evidence of glomerular injury.

The most serious pulmonary complications in this group of patients have been *Pneumocystis carinii* pneumonia, occurring in three patients, two of whom had associated disseminated cytomegalovirus infection. Two of the patients with pneumocystis became ill with normal renal function 10 months and 16 months respectively after transplantation. Cytomegalovirus infection occurred in two additional patients without pneumocystis pneumonia. Both continued to demonstrate the virus even though they remained asymptomatic. The serious nature of these two microorganisms, separate and combined, has been reported.[5,7,21] Herpes simplex, also recognized by others,[16] was most commonly seen in the first three weeks and usually related to the fever associated with the administration of ATG. Warts, considered by Spencer[20] to be associated with viruses, were observed in three patients. Fungal and nocardial infections were recognized but less frequently than that noted by Bach *et al.*[2]

Malignant tumors have been reported in some 7% of all renal transplant recipients[25] with the suggestion that antilymphocyte sera might stimulate the growth of tumors in humans as in animals. The results in this study, although interesting, are too premature for drawing conclusions about the oncologic properties of ALG.

The clinical assessment of ATG in this series of patients, as in those reported by others,[6,11,14,19,22,24] implies that when combined with prednisone and azathioprine, rejection is either avoided or decreased in severity. This statement, although suggestive, cannot be proven conclusively until a double-blind-randomized study has been completed. Such a study still must take into account all of the variables mentioned earlier and analyze the data accordingly. The cadaveric patient, not previously sensitized, appears to be most suitable for such a study.

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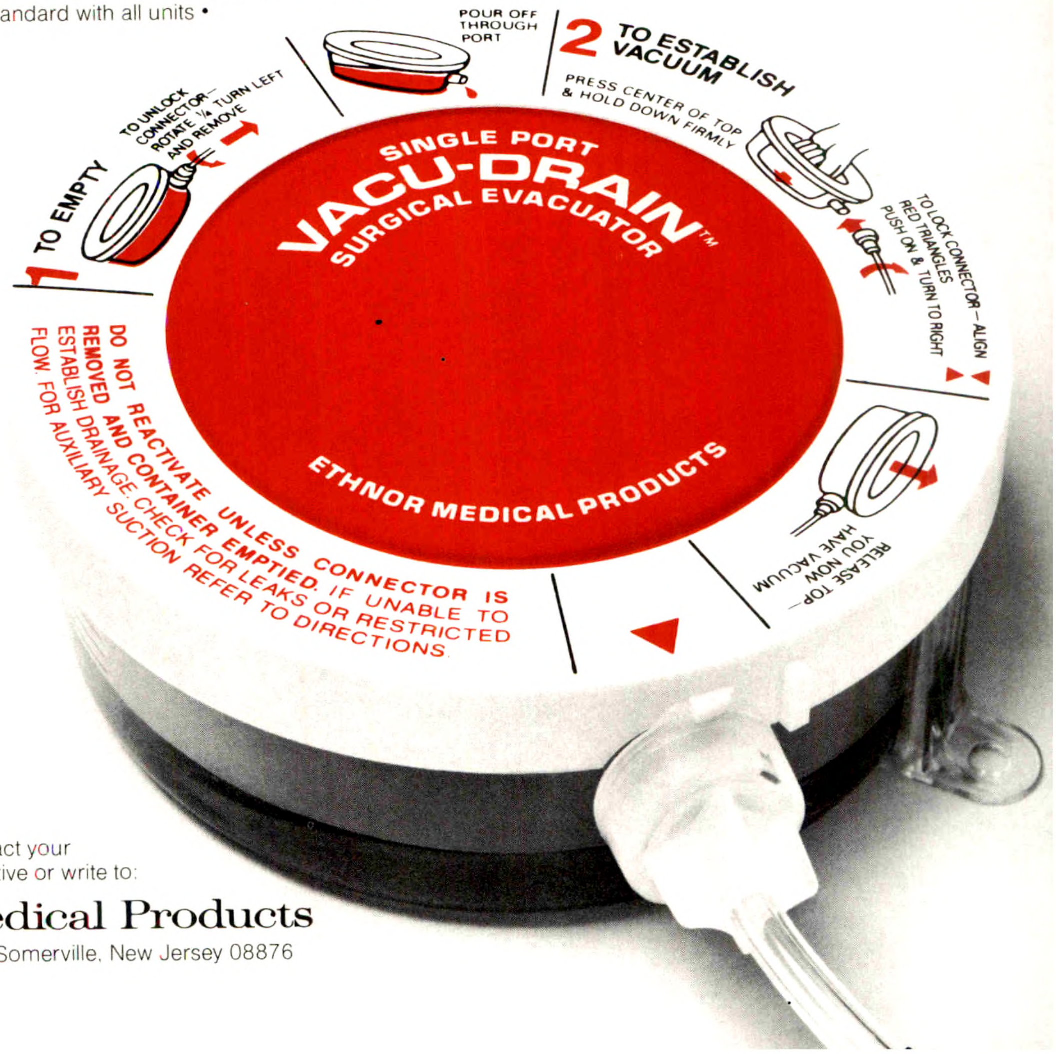
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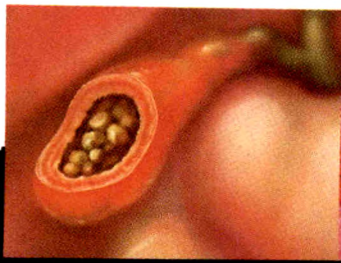
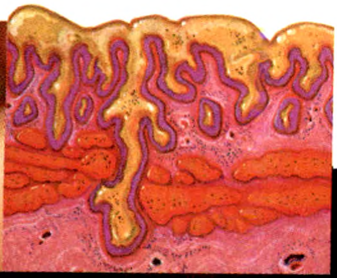
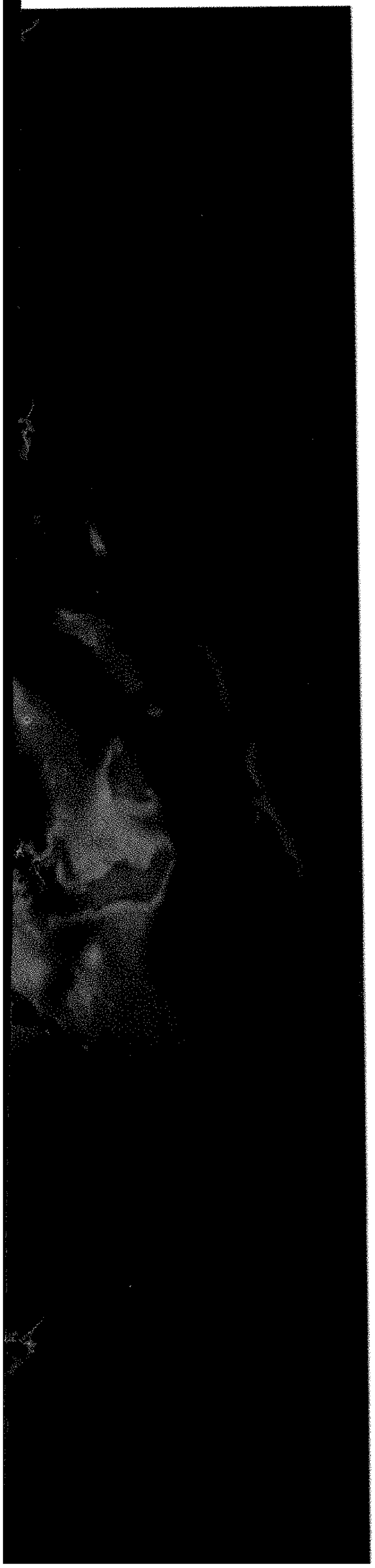




1. Artist's conception of cutaway view of gallbladder containing stones which, by causing irritation of the organ's interior wall and restricting biliary flow, may play a role in the repeated episodes of inflammation and infection associated with chronic cholecystitis.

2. Artist's conception of microscopic section of gallbladder wall showing chronic state with superimposition of inflammation, edema and necrosis due to an acute episode.

A unique view of the gallbladder, from the inside looking out, by means of a true-to-life plastic model.



Cholecystitis from the pathogen's point of view

Vibramycin (doxycycline) penetrates gallbladder tissue to reach susceptible[1] pathogens

Vibramycin can be useful in cholecystitis because it provides a wide antibacterial spectrum and therapeutic tissue concentrations.[2] Vibramycin is active against susceptible[1] strains of bacteria including Escherichia coli and Enterobacter aerogenes (formerly Aerobacter aerogenes).

Concentrations of oral Vibramycin in gallbladder tissue removed from four surgical patients on a dosage of 200 mg. P.O. stat and 100 mg. P.O. once daily until surgery.[2]

Patient No.	Concentration in Tissue (mcg./Gm.)
1	5.80[3]
2	1.58
3	8.68
4	7.73

---

[1] Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

[2] Fabre, J. et al.: Schweiz. Med. Wochenschr. 97:915, May 17, 1967.

[3] Concentration in the bile taken simultaneously: 24.2 mcg./ml.

Vibramycin® I.V.

(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.

200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid.

Pfizer LABORATORIES DIVISION
PFIZER INC

[illegible] side effects and contraindications

Penetrates tissue to reach susceptible[*] pathogens...

Vibramycin® I.V.

(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.
200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid

Important facts about Vibramycin (doxycycline)

- can maintain therapeutic blood levels with a single daily infusion
- can be used without complexities of dosage alteration in patients with impaired renal function
- does not significantly elevate BUN in patients with renal insufficiency
- virtually the same broad range of indications when switching from I.V. to oral form

[*] Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

Vibramycin® Hyclate (doxycycline hyclate) and
Vibramycin® I.V. (doxycycline hyclate for injection)
BRIEF SUMMARY

Contraindicated: In persons hypersensitive to any of the tetracyclines.

Warnings: Use of tetracyclines during the last half of pregnancy, infancy and childhood to the age of 8 years may cause permanent discoloration of developing teeth. This is more common during long-term use of the tetracyclines but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Thus, tetracyclines should not be used in this age group unless other drugs are not likely to be effective or are contraindicated. Individuals receiving tetracycline antibiotics should be advised that direct sunlight or ultraviolet light can cause photosensitivity reactions. If these reactions (exaggerated sunburn) occur, discontinue therapy. Doxycycline forms a stable calcium complex in any bone-forming tissue. Fibula growth has been decreased in prematures given oral tetracyclines 25 mg./kg. q. 6 h., but this reaction was reversible when the drug was discontinued.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur to a significant degree with the use of Vibramycin in patients with impaired renal function.

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus. Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.

Precautions: Overgrowth of nonsusceptible organisms may occur, including fungi. If such superinfections are encountered, discontinue Vibramycin and institute appropriate therapy.

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before initiating therapy. Conduct monthly serological tests for at least 4 months.

Because tetracyclines depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, conduct periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic.

Treat all Group A beta-hemolytic streptococcal infections for at least 10 days.

Avoid giving doxycycline with penicillin because of possible interference with penicillin activity.

Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given concomitantly to patients taking oral Vibramycin.

Adverse Reactions: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, maculopapular and erythematous rashes, exfoliative dermatitis, photosensitivity, urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. Prolonged administration of tetracyclines may produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Bulging fontanels have been reported in young infants on therapeutic dosage but disappeared when the drug was discontinued. A dose-related rise in BUN has been reported.

Oral Adult and Children's Dosages: See the Vibramycin Oral package insert for recommended dosage schedules for adults and children.

Intravenous Dosage and Administration: Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg./day) differs from that of the other tetracyclines (1-2 Gm./day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that Vibramycin, at the usual recommended doses, does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Intravenous Adult Dosage: The usual dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending on the severity of infection, with 200 mg. administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg. daily for at least 10 days.

Intravenous Children's Dosage: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg./lb. of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See "Warning" Section for Usage in Children.)

General: The duration of infusion may vary with the dose (100 to 200 mg. per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg. of a 0.5 mg./ml. solution is one hour. Desired concentrations of the final solution should be 0.2 mg./ml. to 0.5 mg./ml. Concentrations below 0.1 mg./ml. or above 1.0 mg./ml. are not recommended. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly nor subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

More detailed professional information available on request.

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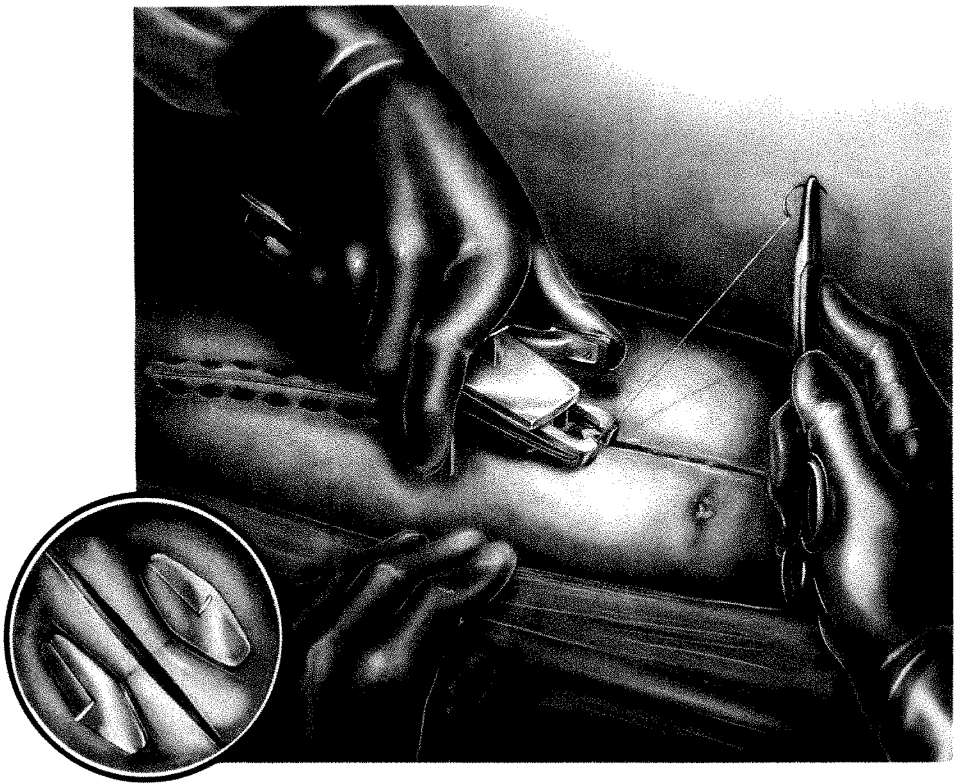

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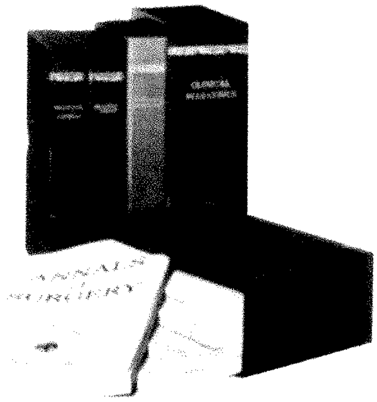

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DESCRIPTION DEXON® polyglycolic acid Suture—Synthetic, Absorbable is a homopolymer of glycolic acid. The sutures are sterile, inert, noncollagenous, nonantigenic, nonpyrogenic, flexible, braided, undyed, with a natural beige color. They are uniform in size and tensile strength, but are smaller in diameter than Absorbable Surgical Sutures of equivalent tensile strength.

ACTIONS When DEXON is placed in tissues a minimal tissue reaction occurs, which is followed by a microscopic layer of fibrous connective tissue which grows into the suture material. Animal studies (subcutaneous tissue in rats, rabbits and dogs) revealed minimal absorption at 7 to 15 days, significant absorption at 30 days, and maximum resorption after 60 to 90 days. Tensile strength, not being a function of the absorption rate, may vary from tissue to tissue, depending in part on the rate of hydrolysis. The early tensile strength of DEXON is reported to be greater than that of comparable chromic catgut. In animal studies (subcutaneous tissue of rats, rabbits and dogs) there occurred a 30 to 50% loss of initial tensile strength in one week and 60 to 80% loss in two weeks, at which time as in the case with chromic catgut no useful residual tensile strength remains.

INDICATIONS DEXON sutures are indicated whenever absorbable sutures and ligatures are employed, provided that extended approximation of tissues is not required or where undue postoperative tension or stress is not anticipated. DEXON is also indicated where non-absorbable sutures are used for their characteristic lack of tissue reaction.

CONTRAINDICATIONS DEXON is contraindicated where extended approximation of tissues under strain must be maintained.

WARNINGS The safe use of this suture in cardiovascular, neural and ophthalmological surgery has not been established. Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon. Do not resterilize. Discard opened, unused sutures.

PRECAUTIONS Acceptable surgical practice should be followed with respect to drainage and closure of infected wounds. DEXON suture knots must be properly placed to be secure. Therefore, place first throw in precise position for final knot, using a double loop, tie second throw square using horizontal tension; additional throws may be used as desired. Skin sutures which remain in place for periods of longer than seven days may cause localized topical irritation and the extended portion of suture may be snipped off after five to seven days, as indicated.

ADVERSE REACTIONS Those reactions that have been reported include tissue reaction or inflammation, fibrous or granulation tissue, wound separation and bleeding and accumulation of fluid around subcuticular stitches.

DOSAGE AND ADMINISTRATION Use as required. Do not resterilize. Discard opened, unused sutures.

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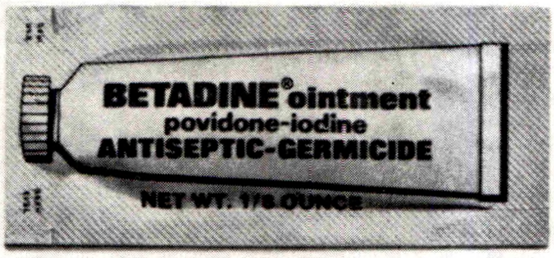

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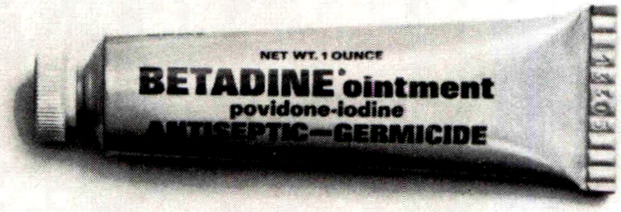

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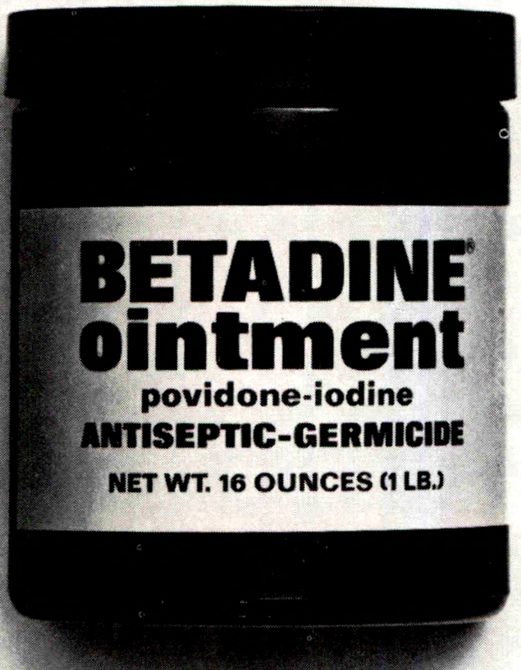

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Kidney Transplantation:

Improvement in Patient and Graft Survival

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MARILENA FOTINO, M.D., ROBERT R. RIGGIO, M.D., JOHN F. SULLIVAN, M.D.,
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From The Rogosin Kidney Center, The New York Hospital-Cornell Medical Center, Departments of Surgery, Pediatrics, and Biochemistry, and the Division of Serology and Genetics, The New York Blood Center, New York, New York

Patient and graft survival were reviewed in a series of 249 kidney transplants done from 1963 to March 1973. Patient survival was calculated by the life table method for the periods 1963–1970, and 1970–1973, since in 1970 a formal Kidney Center was established and mortality rates changed. Graft survival was analyzed in terms of donor source, HL-A matching and immune responsiveness to HL-A antigens. Three-year predicted mortality for cadaver kidney recipients was 62% between 1963 and 1969 (42 patients) and 8% between 1970 and 1973 (67 patients). Similar predicted mortality for related living donors was 30% between 1963 and 1969 (52 patients) and 14% between 1970 and 1973 (85 patients). Mortality has continued to decrease and there has been only one death in the last 87 consecutive transplants, including 57 consecutive cadaver transplants. One-year predicted kidney survival for the 10-year period is 44% for cadaveric, 60% for non HL-A identical related living and 90% for HL-A identical sibling donors. In the cadaver group, those sharing 2 or more HL-A antigens had the same kidney survival as the non HL-A identical related living donor grafts. Since cadaver graft recipients are on dialysis for a longer period of time, immune responsiveness can be detected by their response to blood transfusions, whereas this determination could not be made in our related living donor group. Non-responsive cadaver kidney recipients had 80% one year kidney survival. We conclude that transplant mortality can be reduced to less than 10% by the Center approach to treatment of renal disease, dialysis does not adversely affect future transplantation, and excellent (80%) kidney survival can be expected in properly selected cadaver graft recipients.

Dialysis and transplantation are the only therapies available for patients with end stage kidney disease. Dialysis is a life-saving procedure, and is now widely available in this country and abroad. Properly administered, dialysis can result in rehabilitation for a significant number of patients. Transplantation must be considered, in most cases, an elective procedure. Only in rare instances, when access to the circulation is in jeopardy, may transplantation become an emergency. As an elective procedure, transplantation should be done only when the patient is in optimal physical condition, when there is a reasonable chance of graft success, and when predicted mortality is at least no more, and preferably less than, the mortality of chronic dialysis. If these considerations can be met, then transplantation offers several distinct advantages. The patient has an opportunity of regaining normal kidney function, he can avoid the recurrent and enervating need for thrice weekly dialysis, dietary and fluid restrictions can be removed, anemia, bone disease and neuropathy may be rapidly reversed, growth may occur in children, and the long term costs of treatment are substantially reduced. The latter becomes increasingly important as public monies are used to support the care of patients with end-stage kidney disease.

Despite occasional encouraging reports of low mor-

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Reprint requests: Kurt H. Stenzel, M.D., The New York Hospital-Cornell Medical Medical Center, 525 East 68th Street, New York, New York 10021.

TABLE 1. *Overall Transplant Mortality in First 12 Months*

Year	No. of Transplants	No. of Deaths	% Mortality
1963–1969	93	33	35
1970	34	5	18
1971	47	7	15
1972*	56	3	5
1973† (Jan.-Mar.)	19	0	0

* Minimum followup = 6 months.
† Minimum followup = 3 months.

tality following transplantation,[4,5] the overall experience, as judged by the National Transplant Registry,[14] and other recent reports,[7] indicates an inordinately high death rate from this procedure. The Registry reports 32% cadaver graft recipient mortality and about 16% mortality in recipients of related living donor grafts in the first post-transplant year.

We here report our experience in reducing transplant mortality to less than 10%, indicate some of the factors we think are responsible, and present suggestive data indicating that, with proper donor-recipient selection, 80% cadaver graft survival can be predicted.

Materials and Methods

Two hundred and forty-nine kidney transplants were done between 1963 and March 1973: 141 of these were from related living donors and 108 from non-related donors. Standard surgical procedures were employed, and immunosuppressive therapy consisted primarily of Imuran, 1–3 mg/kg, and prednisolone and methylprednisolone in various dosages. HL-A typing and detection of pre-formed HL-A antibodies to a panel of cells were done as previously described.[13] HL-A responsive individuals were defined as those having repeated strongly positive serological reaction against a variety of different types of lymphocytes. From 1963 to January 1969 the program was relatively small, and patient care was fragmented between medicine, surgery, pediatrics, etc. A Kidney Center was instituted in 1970 to provide patients with comprehensive care for renal disease, and was composed of an interdisciplinary group of internists, surgeons and pediatricians, with, by 1971, a separate hospital floor for renal disease. In-patient and out-patient dialysis facilities were expanded, and affiliations were established with satellite dialysis units throughout the New York Metropolitan area. Patient survival curves were established by the life table method for the period 1963-1969, and for 1970 through March 1973. Kidney survival has not changed appreciably during this time, so the entire series was used to predict kidney survival in the various groups defined: identical sibling donors, non-identical sibling donors and parent to child donors, cadaver donors, cadaver donors sharing two or more antigens, and cadaver recipients who were either responsive or non-responsive to HL-A antigens. The cadaver kidney recipients who shared two or more antigens actually shared only two, in most instances, and all but one of these had one antigen represented at each locus, thus having the possibility of sharing one haplotype.[1]

Patient selection has not changed appreciably from 1963–1973, and, if anything, higher risk patients are now being dialyzed and transplanted.

Results

Patient Survival

Overall patient mortality for each year of the program is shown in Table 1. Table 2 categorizes mortality into related living donor and unrelated donor groups. Using the life table method, predicted patient survival is shown in Fig. 1 for cadaver grafts done from 1963 through 1969, and those done between January 1970 and March, 1973, and in Fig. 2 for related living donor grafts done during the same two time periods. The highest mortality occurs in the first three months after transplantation. There has been a significant decrease in mortality which is greater in the cadaver recipient group than in the related living donor group. The decrease is in two phases; first, there is a decreased mortality in the first 12 months, indicating a decrease in transplant related deaths; and second, there is a flat-

TABLE 2. *Transplant Mortality in First 12 Months: Related Living Donors vs. Cadaver Transplants*

Year	No. Transplants		No. of Deaths		% Mortality	
	Related Living Donor	Cadaver	Related Living Donor	Cadaver	Related Living Donor	Cadaver
1963–1969	52	41	12	21	23	51
1970	22	12	4	2	18	16
1971	27	20	4	3	14	15
1972*	29	27	3	0	10	0
1973† (Jan.–Mar.)	11	8	0	0	0	0

* Minimum followup = 6 months.
† Minimum followup = 3 months.

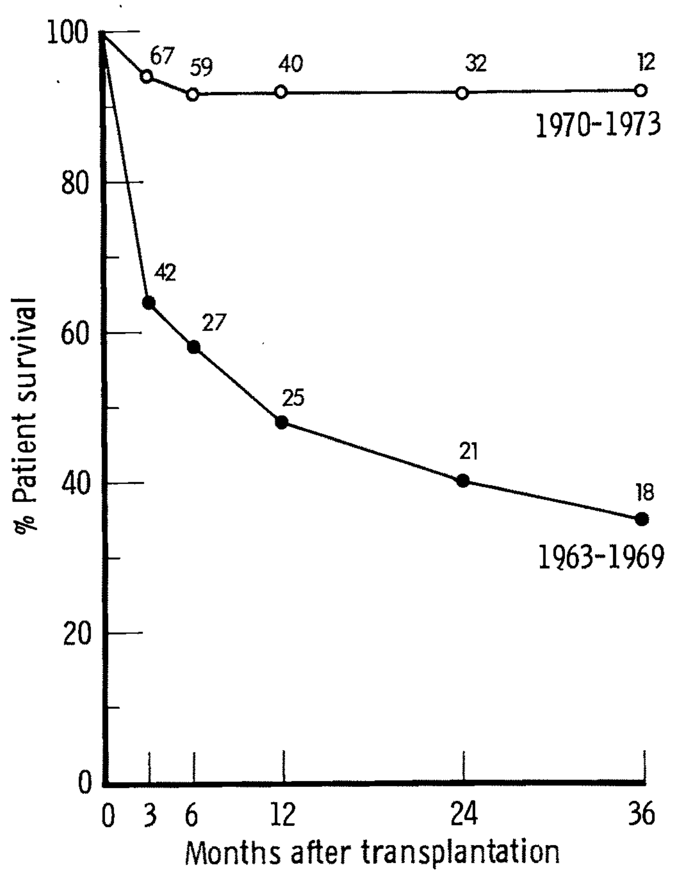

FIG. 1. Predicted patient survival by the life table method for recipients of cadaveric kidney transplants during the periods 1963–1969 ● and 1970–1973 ○. The number indicates the patients at risk at each time period.

tening of the curve after 12 months in the 1970-73 series, indicating, most likely, improved dialysis for patients who rejected kidneys and were returned to chronic dialysis. It should be emphasized that there are no exclusions in these series. Mortality is calculated from the day of transplant onward, and continued even after kidneys have been rejected and the patients are returned to dialysis. Current mortality can be seen to be less for cadaver recipients than for related living donor recipients, and, in fact, there have been no deaths among cadaver recipients in our last 57 consecutive cadaver cases, and only one death in the last 87 cases of our entire series (this includes 19 patients transplanted between April and June 1973).

Cause of Death. Causes of death are indicated in Table 3 for the two time periods. As in other series, the major cause of death is infection. Note the decrease in infectious complications, and especially the virtual absence of fungal infections, since 1970.

Graft Survival. Graft survival was studies as a function of donor source, HL-A typing, and presence or absence of immune responsiveness to HL-A antigens. Recipients of related living donor grafts were divided into two major groups: 1) those with HL-A identical sibling donors; and 2) those with non-identical sibling or parental donors. Figure 3 illustrates the predicted graft survival, by the life table method, for these two groups and for recipients of cadaver grafts. Note that even with identical sibling donors there is a possibility of graft failure. One of these patients had definite rejection, a second was a technical failure, and a third died of fulminant hepatitis. Better graft survival occurs in cadaver kidney recipients who share two or more antigens, as illustrated in Fig. 4, than in those who share 0–1 antigens.[13] This group of cadaver graft recipients has virtually identical kidney survival to recipients of non HL-A identical related living donor grafts.

To determine the status of immune responsiveness to HL-A antigens, patients must be on dialysis for at least 6–12 months.[9] This period gives them an opportunity to be challenged by HL-A antigens in blood transfusions, and thus to manifest possible responsiveness. Related living donor transplants are usually done, at least in our series, before patients have been on dialysis for very long. That is, when patients first become uremic the possibility of related living donor transplant is considered, and, in only 4 or 5 of our living related donor

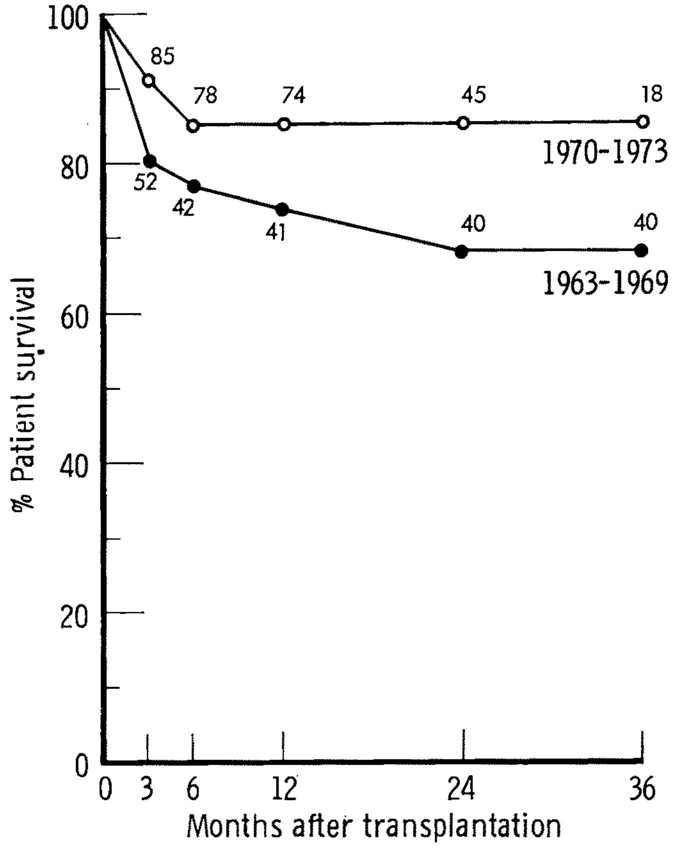

FIG. 2. Predicted patient survival by the life table method for recipients of related living donor grafts during the periods 1963–1969 ● and 1970–1973 ○. The number indicates the patients at risk at each time period.

TABLE 3. *Causes of Death in Transplant Recipients*

Year	No. of Deaths	Infectious Causes of Death			
		Bacterial	Fungal	Viral	Others
1963–1969	33	22 (67%)	6 (18%)	0	5 (15%)
1970–1973	16	7 (44%)	1 (6%)	2 (13%)	5 (31%)

recipients had we prior knowledge of their status of immune responsiveness. We cannot, therefore, construct a meaningful graph of kidney survival in responsive and unresponsive recipients of related living donor kidneys. The situation with cadaver donor recipients is quite different.

Figure 4 illustrates the predicted kidney survival, again by the life table method, for recipients of cadaver grafts sharing 2 or more HL-A antigens (mainly 2). The predicted survival as noted above is the same as that of non-identical familial donors. In the cadaver group, however, we had prior knowledge of their status of immune-responsiveness to HL-A antigens. The top curve in Fig. 4 is the predicted survival of cadaver kidney recipients who share at least 2 HL-A antigens, but who are also immunogically unresponsive to HL-A antigens as herein defined. This group, while small, has significantly better survival than do recipients of non-HL-A identical related living donor grafts.

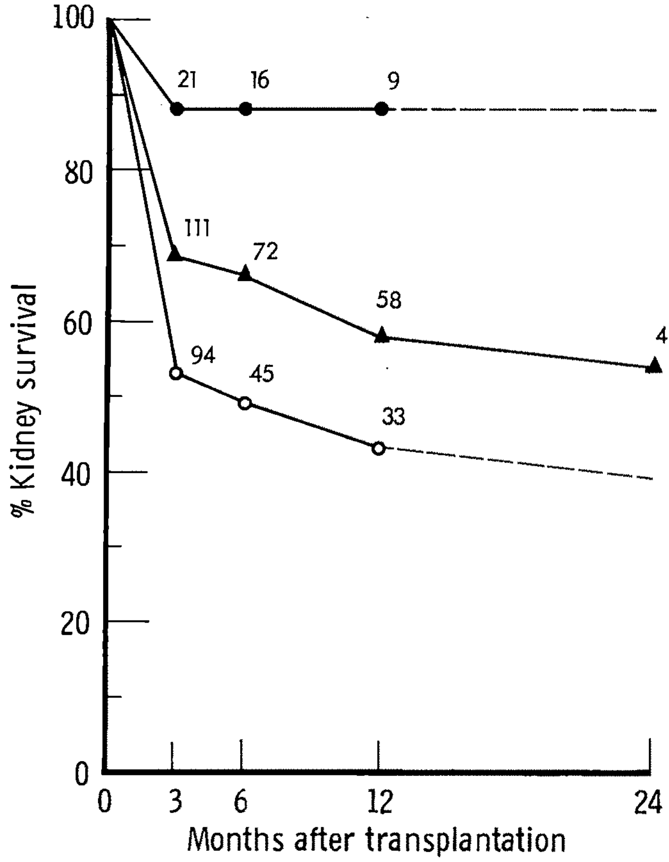

FIG. 3. Predicted kidney survival for HL-A identical siblings ●, non HL-A identical related living donors ▲ and cadaver donors ○. The dotted lines indicate trends with small number of patients at risk.

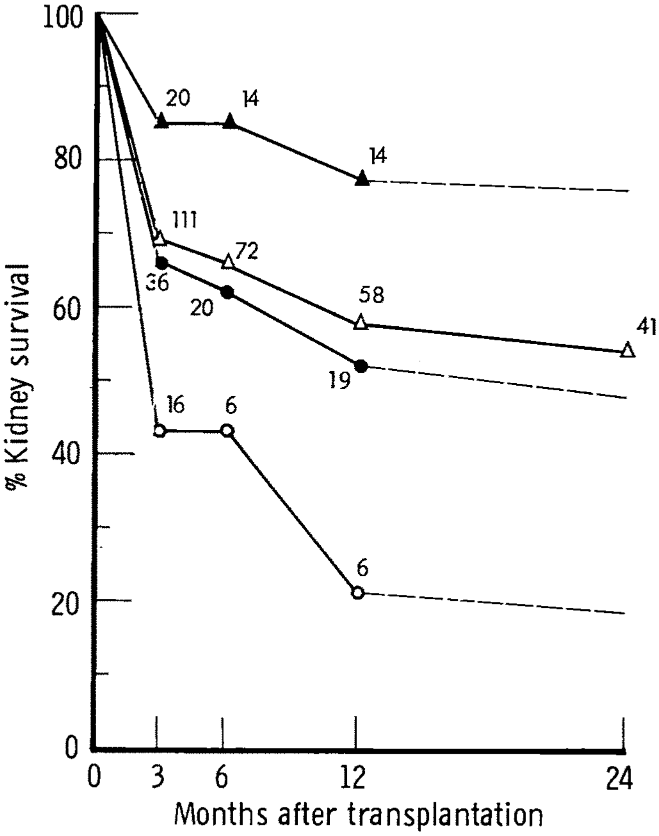

FIG. 4. Predicted kidney survival for non HL-A identical related living donors △, cadaver donors sharing 2 or more antigens (mainly 2) ●, HL-A responsive members ○ and non-responsive members ▲ of this group.

Discussion

Patient survival after transplantation is primarily related to delivery of medical care, whereas graft survival is related to immunological phenomena.

There is no doubt that patient survival can be enhanced, as first shown by Kountz and Belzer,[5] and corroborated by our series. The factors responsible for decreasing mortality are not, however, agreed upon. We doubt if it is simply doing more transplants, since the Registry figures show no difference in patient survival between large and small centers. The factors in our series that were temporally related to a decreased mortality, and that we consider significant, are the following:

1) Creation of a formal interdisciplinary kidney center with a full range of treatment and diagnostic facilities, including in-patient and out-patient areas, and affiliation with satellite dialysis units. These facilities ensure proper patient preparation, rapid return to chronic dialysis if the transplant fails,

and a continuity in care that gives the patient with end-stage renal disease a feeling of confidence and optimism. The center staff becomes highly skilled in the management of dialysis and transplant problems; areas where fastidious attention to technique and detail are of paramount importance. It is difficult to quantitate the advantages of the Center approach, other than to simply point out the association with a remarkable decrease in patient mortality.

2) Related to the creation of the Kidney Center is a current policy of early removal of non-functioning kidneys, and limiting dosages of immunosuppressive drugs. When adequate dialysis facilities are available, the decision to remove a marginally functioning kidney is an easy one.

These two interrelated factors are, we feel, of critical importance in delivery of medical care to the patient with end-stage kidney disease. There should, therefore, be no difference in patient survival after related living donor or cadaver transplantation. Our slightly higher mortality in the related donor groups is quite possibly due to patient selection. Nearly all the patients who died since 1970 had some medical problems associated with dialysis that prompted rapid transplantation from an available family donor.

Kidney survival depends on more scientifically ascertainable parameters. Antigenic strength and individual immune responsiveness to particular antigenic stimuli are the two major factors that govern host response to foreign materials. In clinical transplantation the former can be controlled, at least partially, by choosing donor kidneys that share as many antigens as possible with the recipient. Our results, as well as others,[10,15] certainly indicate that HL-A matching is important in both related living donor and cadaver transplantation. Responsiveness is a more subtle problem and may be considered in two general categories. First, overall response of the entire immune system. This general response can be blunted by cytotoxic agents, probably by adrenocortical hormones, by anti-lymphocytic sera, and by systemic diseases that lead to general debilitation and inanition. The second category is a genetically determined ability to respond to particular groups of antigens. The best demonstration of this phenomenon is in guinea pigs that can be bred to eliminate the response to particular materials.[8] Immune responsiveness to HL-A antigens among transplant recipients is an important determinant of long term kidney function.[12]

Our results show that non-identical familial donor recipients and reasonably well matched cadaver recipients have virtually identical long term graft survival. However, there are no techniques currently available to determine a patient's innate immune responsiveness to HL-A antigens other than by challenging him with these antigens. Since most related living donor grafts are done prior to extended dialysis, we cannot identify the responsive individuals in this group. Cadaver recipients, on the other hand, generally have long waiting periods on dialysis and consequently have an opportunity to become sensitized. The identical kidney survival in these two groups, without taking responsiveness into consideration, leads us to believe that sensitization by transfusions merely indicates immune responsiveness, and does not alter the chances of graft success. This, of course, presupposes that crossmatches are always done, and that no patients receive kidneys with positive cross matches. Thus, fewer kidneys will be available for this group, and there will be a longer waiting time on dialysis, at least with the current availability of cadaver kidneys. Nevertheless, by prior identification of the responsive group, better results can be achieved. The non-responsive group will do well with only a reasonably matched kidney (2 antigens in common), whereas the responsive group should wait until a 2 or 4 antigen match is available.[11] Since transfusions are being used with much less frequency now during chronic dialysis, it will become of great importance to develop meaningful *in vitro* techniques for assessing immune responsiveness. Challenge of the host with HL-A antigens would then not be necessary. Advances in typing and immunosuppressive techniques would also modify this problem in the future.

These results have practical significance in several areas. First, 3 year mortality can be decreased to less than 10% and probably to 5%, by developing interdisciplinary centers for the treatment of renal disease. This is certainly less than the mortality of unselected patients on chronic dialysis.[3] The critical aspects in reducing mortality are: ready availability of dialysis, prompt removal of marginally functioning kidneys, limiting dosages of corticosteroids and continuity of patient care as can only be achieved in an interdisciplinary center. Second, if prior knowledge of immune responsiveness can be gained, cadaver kidneys can be utilized in a more effective way. Those non-responsive individuals will have an 80% graft survival with only reasonably matched kidneys, whereas very close matching should be sought for responsive individuals. Given these factors, it becomes vitally important to develop and implement regional cooperation in organ sharing in order to have enough patients and donors to select the proper match. A major research goal should be to develop an *in vitro* test for immune responsiveness to HL-A antigens. Third, in contrast to a recent report,[2] length of time on dialysis does not appear to mitigate in any way against future transplantation. This observation has recently been confirmed by others.[6] With our current state of knowledge, the possibility of sensitization to HL-A antigens allows us to identify responsiveness and non-responsive individuals. Fourth, the common view that survival is greater for a patient on home dialysis or receiving a related living donor transplant, as opposed to receiving a cadaveric kidney,[7] is not necessarily so. Finally, if sufficient cadaver organs could be made available, there would be no indication to use related living donors except, perhaps, carefully selected identical siblings.

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Femoropoliteal Bypass Graft Patency:

An Analysis of 156 Cases

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Patency rates were unrelated to severity of ischemia, to run-off, to presence of diabetes, and to diameter of vein in 156 femoropopliteal bypass grafts with saphenous vein followed from 9 to 106 months.

SINCE 1949, when Kunlin[8] introduced the femoropopliteal bypass graft with saphenous vein, several centers have reported their results. Patency rates at 30 days have varied from 76%[5] to 96%.[13] Cumulative five-year patency has varied from 60% to 78%.[4,5]

Linton and Darling[4] believe technical errors at the time of operation account for both early and late failures, and there is general agreement that technical factors account at least for early failures. Some authors[6,12,16] report an adverse effect of diabetes on patency whereas others[1,9] report no adverse effect. Some writers[5,9] believe clinical severity of ischmia influences graft failure whereas others[7,13] believe the severity of ischemia has little to do with patency. Some [5,10] believe failure is more likely in the present of poor run-off whereas others[4,7] believe run-off does not affect patency. Most authors[7,11,13,14] believe small veins are apt to occlude.

This paper relates patency to clinical severity of ischemia, to run-off, to diabetes and to diameter of vein in 156 consecutive grafts implanted from June 1962 to January 1972, in 123 patients ranging in age from 30 to 92 with an average age of 63.

Methods and Clinical Material

Data were placed on keysort cards containing 64 factors relating to the femoropopliteal bypass graft with saphenous vein.

Gehan, with a computer program, estimated the patency curves of grafts using Kaplan and Meier's method.[2] This method is superior to the life table method, especially for samples of less than 50. Patency curves were done for the entire group and for subgroups including diabetics, various clinical and arteriographic degrees of ischemia, and various graft diameters. He tested differences between curves with a modification of the Wilcoxin test.[3]

Associated diseases were common. Aortoiliac disease was present in one-fourth; however, it was severe enough to necessitate aortofemoral bypass grafting in only 16 patients. Arteriosclerotic heart disease previously manifested by myocardial infarction, angina, or congestive heart failure existed in one-third. Five per cent had a history of stroke—none had significant residual symptoms. One-third had blood pressures higher than 140/90. Thirty-one per cent had diabetes mellitus. Most of the patients were cigarette smokers and various degrees of chronic obstructive pulmonary disease were common.

Forty-three per cent of the procedures were done for intermittent claudication, 25% for rest pain, and 32% for ischemic ulcer or gangrene. All patients had absent popliteal and pedal pulses preoperatively, and femoral arteriograms demonstrated obstruction. Most grafts were placed from the common femoral to distal popliteal arteries using Szilagyi's[15] method. Reversed saphenous vein grafts were used for all procedures. Proximal anastomosis was to the common femoral artery in 117 cases,

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to the deep femoral in 21 and to the superficial femoral in 15. Distal anastomosis was to the distal popliteal in 135 cases; in 16 the graft was anastomosed distally to the tibial or peroneal arteries.

Mortality and Morbidity

Deaths related to the operation occurred in two patients. The first, a 75-year-old man with gangrene of the toes, died suddenly on the first postoperative day. Necropsy revealed extensive coronary disease and it was presumed that ventricular fibrillation had occurred. The second patient was 57 years old and death on the eighth postoperative day was due to an acute myocardial infarction, confirmed at necropsy.

Eight patients were returned to the operating room on the day of operation, three for correction of occlusions and five for bleeding. Two more developed hematomas. Bleeding has been rare since beginning routine use of protamine at the end of the procedure to counteract the effect of heparin. Skin necrosis, usually after undermining, resulted in delayed skin healing in a few cases. Wound complications never resulted in occlusion of the graft. In two patients the graft became stenosed 18 months and 11 months after operation due to inadvertent clamping of the saphenous vein during removal; in a third a subintimal plaque stenosed the graft. Extrinsic fibrosis, probably due to a hematoma and drainage, stenosed the graft in another. All four were remedied with vein patch angioplasties. Vein patch angioplasty to one graft only 3 mm in diameter was necessary on the day of operation to correct early occlusion.

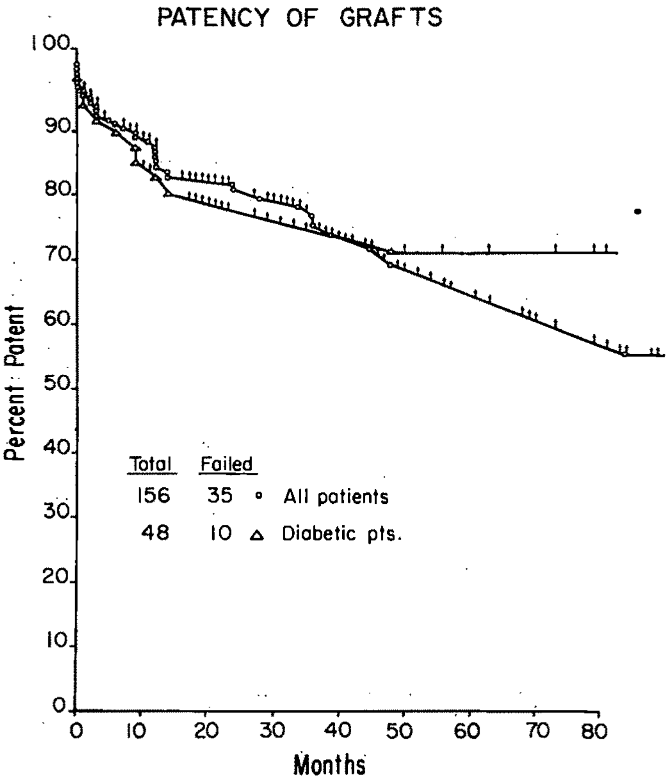

FIG. 1. Computer-drawn curve for all grafts and for diabetics.

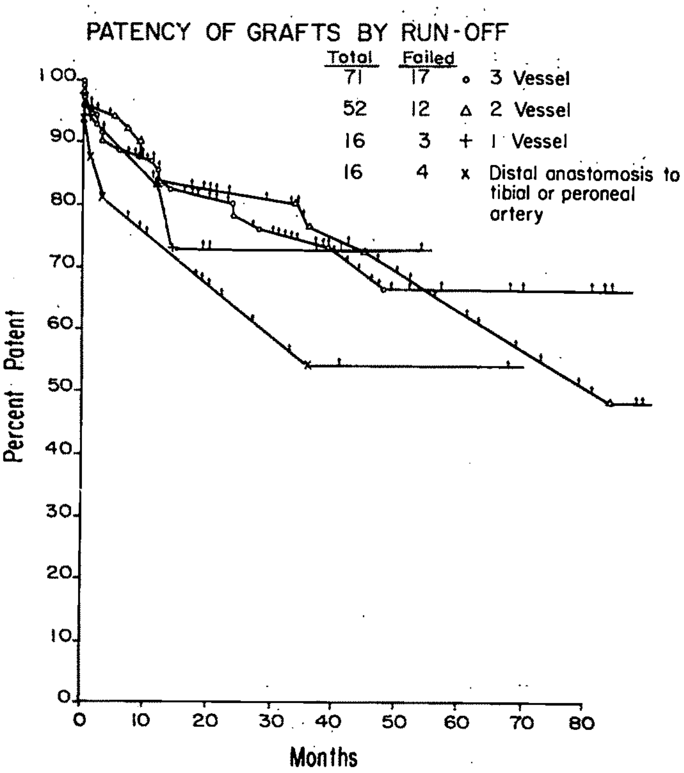

FIG. 2. Computer-drawn curves for grafts according to arteriographic status of run-off.

Patency

A good popliteal pulse was considered adequate evidence of an open graft. Thirty days postoperatively all except two had patent grafts for a 98% early patency rate. I have examined all patients each year postoperatively except two who moved away and were lost to followup at one year. Fifty-six late postoperative arteriograms done from 3 months to 8 years after operation show no aneurysmal formation, calcification, or degeneration in the graft.

Ninety limbs have open grafts and 38 grafts were open at the time the patient was last seen prior to death. Twenty-eight occluded with regression of the limb to preoperative status; none which closed resulted in a condition worse than preoperatively. In two cases the bypass graft only temporarily halted advancing gangrene, and above knee amputations were necessary when the graft occluded.

Status of inflow does not seem too important. Two patients in this series have an open graft distal to an occluded iliac artery. Bypass grafts were placed in the presence of minimal to moderate degrees of iliac disease, particularly in elderly poor risk patients.

Figure 1 shows a computer drawn plot of the patency curve of all grafts. The circles on the curve indicate points in time where a failure occurred. The small daggers above the curve represent censored observations, that is, lengths of time over which grafts have remained functional. The median estimated patency time has not yet been reached but the curve suggests that it will be greater than 7 years. The estimated percentage of patients with grafts open longer than 1 year is 84%, and longer than 5 years is 65%. One graft is still functional after 106 months, but this time was out of range of the curve and is not indicated. The patency curve for the 48 diabetic patients also appears in Fig. 1, and is similar to the curve for all patients.

In Fig. 2, the patients were grouped by number of run-off vessels, and graft patency curves were calculated for each group. Seventy-one popliteal arteries had three open branches (3 vessel run-off); 52 popliteal arteries had two branchs open (2 vessel run-off); and 16 popliteal arteries had only one branch open (1 vessel run-off). In 16 cases the popliteal artery was occluded necessitating distal anastomosis to the tibial or peroneal vessels. The curve for this group is below all other groups; three failures occurred within three months in these patients. There are no statistically significant differences among any of the curves (P-value > .10 for all comparisons by Wilcoxin test).

Figure 3 plots graft-patency curves with patients grouped by degree of ischemia. The plot of the patency curve for grafts in patients having ischemic ulcer or gangrene is below that of the other two groups. Comparison of this curve with that for patients having rest pain resulted in P = .09, which suggests that there may be a real difference in patency of grafts in the two groups. The patency rate of grafts in patients having claudication falls between these two groups and is not significantly different from either one.

Patients were also classified by diameter of grafts and patency curves are plotted for these groups in Fig. 4. There is no evidence here of a statistically significant difference in length of patency based on diameter of graft.

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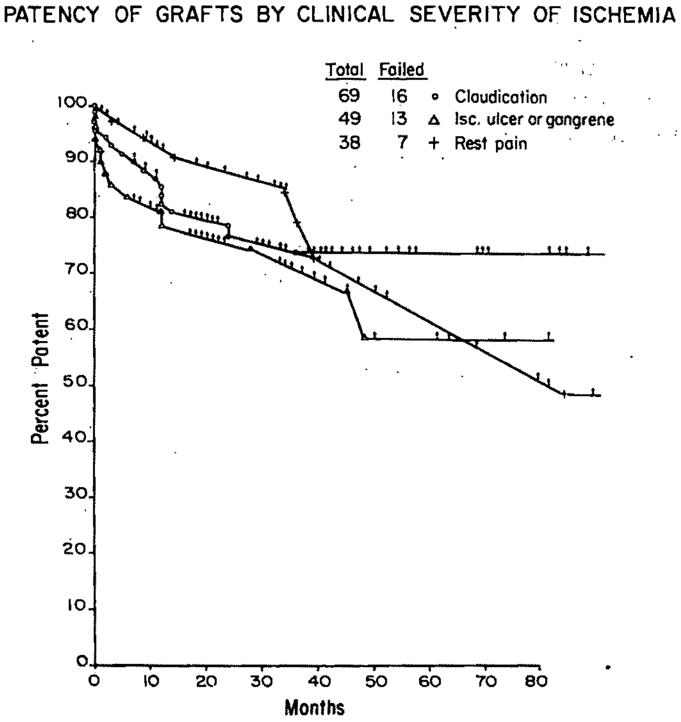

FIG. 3. Computer-drawn curves relating clinical severity of ischemia to patency rates.

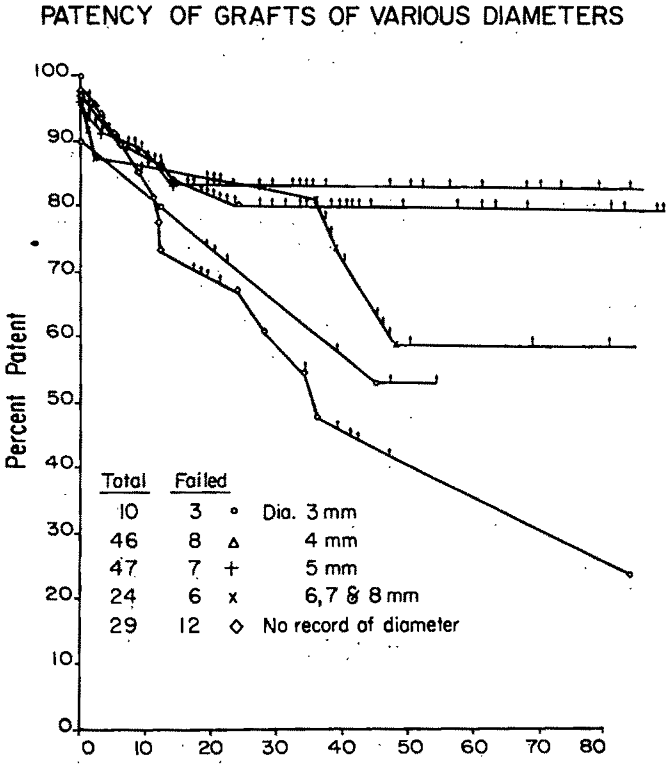

FIG. 4. Computer-drawn curves relating patency to diameter of grafts at their most narrow segment.

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Critical Arterial Stenosis:

A Theoretical and Experimental Solution

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The mechanics of critical stenosis of a blood vessel are studied by means of a comprehensive theoretical model in terms of energy changes and dissipation. These theoretical assumptions correlate well with experimental data obtained in vivo. Previous work in this field is analyzed. This new treatment of the phenomenon of blood vessel stenosis allows explanation of apparent contradictions in previous studies. When the velocity of flow in the unstenosed portion and the geometry of the stenosis are known, the drop in pressure at flow can be predicted.

THE FUNCTIONAL SIGNIFICANCE of the narrowing in an arterial segment is a central problem in cardiovascular pathology. For many years, since Mann's original work,[7] it has been known that a substantial decrease in the lumen of a vessel must occur before a drop in pressure or flow can be measured distal to the narrowed point. It is also well known that beyond a certain degree of constriction, small decrements in the area result in abrupt changes of pressure and flow distal to the constriction. The cross-sectional area value beyond which this phenomenon occurs has been termed the "critical" area of a stenosis (Fig. 1).

This term, however, has been defined in different ways; some arbitrary, some contradictory. Most workers[3,4,12] describe this "critical" area as that beyond which small decreases in vessel lumen areas will result in significant or "marked" effects in pressure drop or flow-rate decrease beyond the stenosis. Others, such as Brice,[1] have adopted an arbitrary definition; ". . . that constriction which would produce a 5% fall in distal mean pressure or a 10% decrease in distal mean flow." Under certain conditions, such as high flow rates, the above definitions may represent substantially different values than the one that would be obtained by Weale's standard ". . . that cross-sectional area at which 80% of the pressure gradient obtainable on total occlusion occurs."

The problem of explaining what happens in a critical stenosis has been approached following basically three lines, or any combination of them: mathematical models, physical models of the circulation and experimentation in animal or human subjects (biological models). The pitfalls inherent in physical and biological simulation have led some workers to make conclusions that are often incomplete and sometimes incorrect. Thus, for some workers, the critical stenosis value would be defined by the percentage reduction of the area at the stenosis site.[7] For others,[1,4] the factors determining the critical value would be the absolute cross-section of the stenosis and the value of the "peripheral resistance," while they claim that the area of the un-stenosed portion of the vessel bears no relation to the value of the critical area. Lastly, others[8] insist that the most important factors in determining the value of the critical area are the velocity of the flow in the unobstructed segment and the area ratio between the former segment and the stenosis. Clearly, there is a fair amount of confusion around the question of which are the parameters that define the "critical" value of narrowing that will produce

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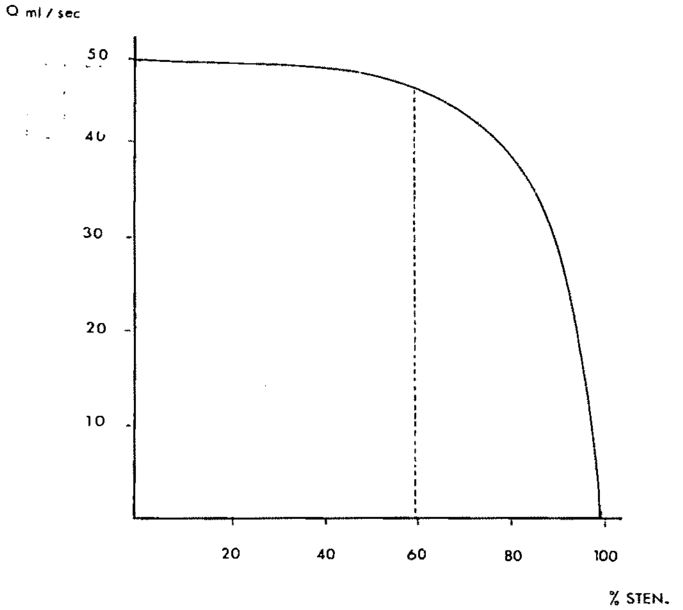

FIG. 1. The phenomenon of critical arterial stenosis. Flow rates plotted versus percentage stenosis of vessel lumen.

a significant pressure gradient or a drop in the flow rate through a vessel.

The problem of the critical stenosis, the prediction of its occurrence and the physical grasp of its mechanics are not therefore theoretical or abstract problems, but matters that have a direct importance on everyday surgical decisions and planning. Narrowing of an artery is the most common problem in our circulatory system beyond middle age and, a very common reason for which vascular surgery operations are performed. Having established its importance, its elucidation must be pursued for, being a problem of fluid mechanics, however particular, it must have a theoretical solution.

Theoretical Solution

Kinetic Energy and the Area Ratio of the Constriction

Our approach has been to describe the circulatory phenomenon in terms of its cause: energy gradients causing blood mass displacements from a high to a low energy point (the traditional proposition that blood flows from a high to a low pressure point is only a specific case of this general proposition).

We shall recall briefly that the total energy (Et) in a unit weight of blood can be expressed as the sum of three components $Et = h + V^2/2g + P/\gamma$ where the term h is the gravitational potential energy, $V^2/2g$ is the kinetic energy (Ek) and P/γ is the lateral pressure energy (Ep). In as much as we shall be considering vessels in a horizontal position, the gravitational component (h) can be neglected.

To calculate the total energy across an arterial segment, all we need to know is the geometry involved, and the values of the systemic pressure (P) and its bulk velocity (V). The pressure (P) can be measured directly and the velocity (V) can be obtained from the volume flow rate (Q), since $V = Q/A$. These data (P, A) can be measured in both the pre (P_1V_1) and post (P_2V_2) stenotic segments, from where the values of P and V at the stenosis site ($P_{s1}V_s$) can be computed once the geometry of the arterial segment is known.

Let us consider (Fig. 2) a continuous arterial segment of known geometry which is divided into three sections, 1 (pre-stenotic), S (stenotic) and 2 (post stenotic). The velocity at the stenosis (V_s) can be computed as follows:

$$\begin{Bmatrix} Q_1 = A_1V_1 \\ Q_s = A_sV_s \end{Bmatrix} \qquad [1]$$

$$A_1 - A_s = \pi(r_1^2 - r_s^2) = \Delta A \qquad [2]$$

from [2] and [1]:

$$\frac{Q_s}{Q_1} = \left(\frac{A_s}{A_1}\right)\left(\frac{V_s}{V_1}\right) = \left(1 - \frac{\Delta A}{A_1}\right)\frac{V_s}{V_1}\,;$$

solving for V_s:

$$V_s = V_1\frac{1}{\left(1 - \dfrac{\Delta A}{A_1}\right)} = V_1\,\frac{1}{(r_s/r_1)^2}\,;$$

substituting for $\omega = r_s/r_s$,

$$V_s = V_1 \cdot \omega^{-2} \qquad [3]$$

From the value of V_s, the corresponding value of kinetic energy at the stenosis (Ek_s) can be derived since: $Ek_s = \frac{1}{2}m \cdot V_s^2$

$$\begin{Bmatrix} Ek_s = \dfrac{\rho}{2}A_sV_s^3 \\ Ek_1 = \dfrac{\rho}{2}A_1V_1^3 \end{Bmatrix}, \qquad [4]$$

where P is the density of the fluid

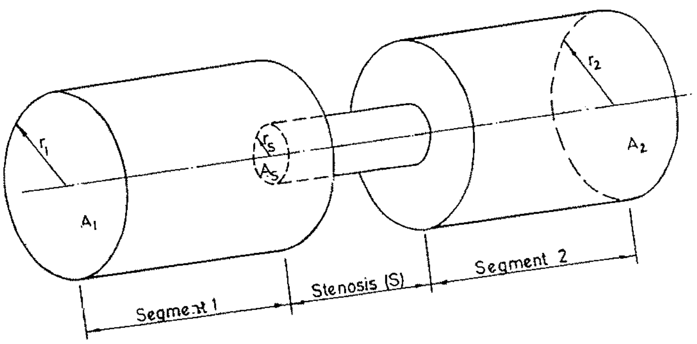

FIG. 2. Schematic representation of the stenosis model with the three segments under consideration (1, S and 2). Flow direction 1 → 2.

$$\frac{Ek_s}{Ek_1} = \frac{A_sV_s^3}{A_1V_1^3} ;$$

and substituting by [3]:

$$\frac{Ek_s}{Ek_1} = \omega^{-4} \qquad [5]$$

Figure 3 is a graphical representation of this function which states that the ratio of kinetic energy in the stenosed segment (Ek_s) to kinetic energy in the prestenotic segment (Ek_1) is a fourth power function of the decrease in the radius of the vessel.*

Let us assume a stenosis of minimal length whose physical approximation could be the constriction caused by a tight suture around a vessel (see experimental device in Fig. 6). If we now plot the ratio Ek_s/Ek_1 for this constriction, versus the values of ω (that is the ratio of radii) we obtain the curve displayed in Fig. 3. Due to the effect of the fourth power function, a sharply increasing amount of kinetic energy is required to "carry" the flow through the stenosis (Ek_s). Now, the total energy in the stenosis segment ($Ek_s + Ep_s$) cannot be greater than the energy in the prestenotic segment; thus, if Ek_s is increased, then Ep_s must decrease. Hence a drop in lateral pressure energy is inevitable as the kinetic energy through the stenosis increases. In fact, as ω approaches zero, a great deal of pressure energy (Ep) must be converted at an accelerated rate into kinetic energy in order to maintain flow through the stenosis.

Evidently, as the demand for kinetic energy in the stenosis increases with progressive reduction of the stenotic area, a point will be reached when the remaining pressure energy can no longer meet the demand. At this point the flow through the stenosis will have to "slow down." This also implies a decrease in velocity at the prestenotic segment, ΔV_1, and hence a decrease in the flow rate ΔQ_2.

Normally, the fraction of energy being used as kinetic energy in a peripheral medium-sized artery is rather small and less than 1% of the total energy† during peak systole. As the stenosis progresses, the graphic representation of the function $Ek_s/Ek_1 = \omega^{-4}$ (Fig. 3) shows that Ek_s has to rise considerably before its magnitude becomes appreciable (Ek_1) being originally so small). From this point on, as Ek_s increases drastically at an exponential rate, a correspondingly speedy fall in pressure and flow will occur.

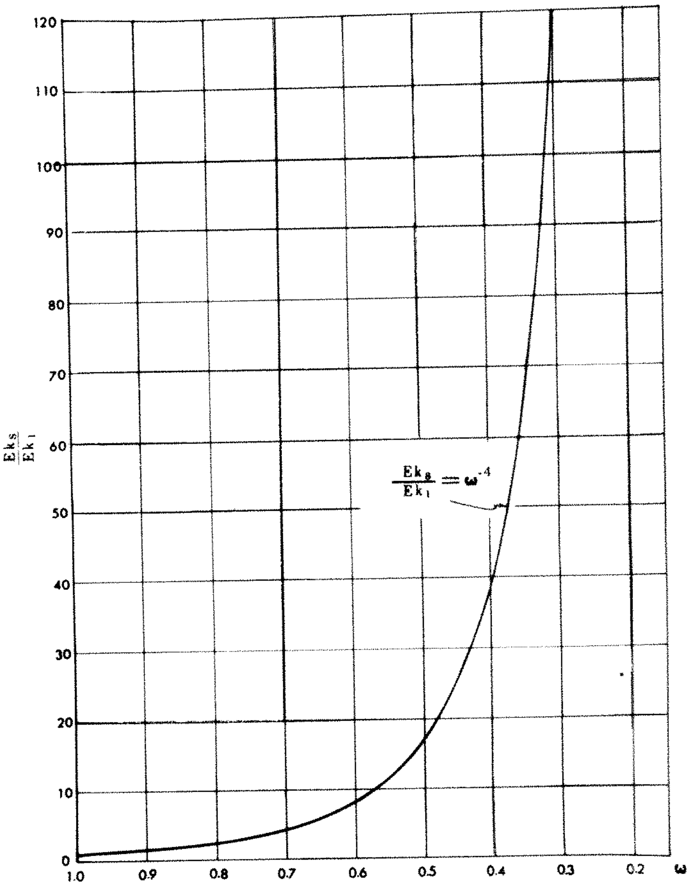

FIG. 3. Graphic representation of the ratio Ek_s/Ek_1 plotted versus the ratio of radii (ω).

According to the Bernoulli principle, an "ideal" fluid will not generate a pressure gradient across a stenosis but a transfer of energy from one form to another ($Ep_1 \rightarrow Ek_S \rightarrow Ep_2$). However, the simple fact that, in a viscous fluid flowing through a tight stenosis, an otherwise laminated flow gives rise to a turbulent jet, (which is later dissipated in the distal stream as heat) indicates that energy must be lost in the process. That blood flowing through a tight stenosis results in a turbulent jet which quickly dies out in the distal segment is beyond doubt: this phenomenon can be observed with the naked eye and, more precisely, with high speed cinematography.

Application of Conventional Hydraulic Principles to the Problem of Stenosis

Normally, in a continuous conduit having a contracted segment, the transfer of lateral pressure energy to kinetic energy in the contraction ($Ep_1 \rightarrow Ek_s$) is made with relatively little energy loss. Conversely, the transfer of kinetic energy to lateral pressure energy ($Ek_s \rightarrow Ep_2$) at the expansion of a conduit is a very expensive one (in terms of energy). Energy is lost in the expanded area by the formation and maintenance of vortices and in providing the viscous drag which slows down the jet. These energy losses are usually accounted by as contraction loss (h_c) and expansion loss (h_e) as the fluid enters and leaves the stenosis respectively.

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* The theoretical errors that may be incurred in the computation of kinetic energy from mean velocities as opposed to doing so by differentiation of elements are discussed in the Appendix.

† See appendix.

Expansion Loss. Energy loss due to sudden expansion has a common place in hydraulics where—for the particular case of sudden expansion in a pipe—the following formula is used:[6]

$$h_e = \frac{(V_s - V_2)^2}{2g} \qquad [6]$$

This equation is used in hydraulic engineering where flow in pipes is generally considered to be under turbulent conditions. In our case where a high speed jet discharges into a relatively slow moving fluid mass (poststenotic segment) the use of this formula seems to be justified. Figure 4 illustrates the flow profile of a stenosis in a photograph obtained from a flow model (based on the Hele-Shaw theory). If we now insert this term h_e (Eq. 6) into the continuity equation derived from Bernoulli's principle:

$$P_s/\gamma + V_s^2/2g = P_2/\gamma + V_2^2/2g + h_e,$$

we have:

$$P_s/\gamma + V_s^2/2g = P_2/\gamma + V_2^2/2g + V_s^2/2g - V_2^2/2g - 2V_sV_2/2g;$$

$$P_s/\gamma = P_2/\gamma + V_2^2/g - V_sV_2/g$$

Neither in the work presented in this paper nor from the data from Fry is there any evidence to suggest that the loss in lateral pressure energy that occurs at stenosis is regained in any substantial amount in the post stenotic segment. In other words:

$$P_s/\gamma \simeq P_2/\gamma \qquad [7]$$

and therefore the term $V_2^2 - V_sV_2/g$ must be very small. For practical cases, this means that the lateral pressure energy at the stenosis is approximately the same as the lateral pressure energy in the post-stenotic segment ($Ep_s \simeq Ep_2$). Thus, the kinetic energy involved in carrying the flow through the stenosis is lost at the sudden expansion in the formation and maintenance of local turbulence (it is possible, however, that in an elastic system, such as an artery, a small amount of pressure recovery could occur). The conventional representation of the increase in lateral pressure energy at the post-stenotic segment does not really apply to turbulent viscous flow, which is the case of a critical arterial stenosis. The loss in lateral pressure energy that occurs at the stenosis is mostly non-recoverable in the post-stenotic segment.

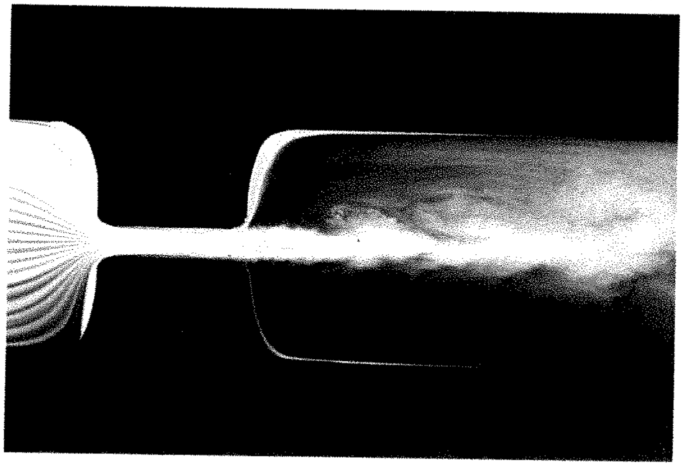

FIG. 4. Photograph of flow through a stenosis taken using the author's flow model (based on the Hele-Shaw theory). The laminar flow in the prestenotic segment remains laminated through the stenosis. At the outlet, a disturbed flow pattern is noted immediately distal to the stenosis. In the post-stenotic segment the energy loss (i.e. expansion loss) through eddies is obvious.

Contraction Loss. The energy loss due to a sudden contraction in a pipe is usually much smaller than the corresponding expansion loss. There is also a common hydraulic formula for this loss[6] $h_c = 0.5\ V_s^2/2g$. This empirical formula however is not applicable to our problem because: 1) the flow condition proximal to a stenosis in an artery is quasi laminar, while the hydraulic formula is the result of experiments performed in turbulent pipe flow. At the inlet of the stenosis most of the contraction loss occurs in the boundary layer, the characteristics of which will vary greatly between quasi laminar and turbulent flow conditions;[11] 2) this hydraulic formula is commonly used to calculate the contraction loss in water pipes. The geometrical reduction in area of water piper that normally takes place is, in practical terms, of much lesser magnitude than the one under consideration here: a critical stenosis.

Fraction Loss through the Stenosis. The pressure drop or flow decrease in a stenosis is also known to be a function of its length. It is primarily the result of fraction forces that develop between the moving fluid and the wall boundary. For a steady flow system—laminar or turbulent—this loss of energy through length is expressed by the Darcy-Weisbach formula:[9]

$$h_L = f\,\frac{L}{D}\,\frac{V^2}{2g} \qquad [8]$$

(f) being a coefficient (Darcy-Weisbach resistance coefficient) that varies with the Reynolds number, (L) length of the segment (in our case, the length of the stenotic segment), (D) diameter of the conduit and ($V^2/2g$) the kinetic energy per unit weight of the fluid flowing through the segment under consideration.

It is obvious that in a stenosis this friction loss will be directly proportional to the length and to the kinetic energy of the blood flowing through it, and inversely proportional to the diameter of the vessel. The graph of the energy loss as a function of the length of the stenosis, can therefore be anticipated to be a curve whose slope will become steeper as the internal radius of the stenotic area under consideration decreases.

Experimental Method

Experiments were carried out in greyhound dogs. Anaesthesia was obtained with intravenous Nembutal (1 mg/kg weight) and the animals were systemically heparinized with 5,000 units of heparin. The iliofemoral trunk was dissected and collateral vessels were ligated with the exception of the internal iliac and the saphenous arteries; these were used as side branches and connected by 13 cm of plastic tubing to pressure transducers (Bell & Howell L 221) (Fig. 5). The pressure transducers were calibrated against a mercury column at the beginning and end of each experimental run. The external diameter of the exposed arterial segment was measured in three points using both a vernier caliper and a fine suture to determine the circumference of the vessel. Two of these points of known external diameter were chosen for the placement of suitable electromagnetic flow probes; the third (middle) point was the site elected for placement of the constricting device. The electromagnetic flowmeter used was the Nycotron 372 with cuff probes, type PS. Occlusion zero was obtained before every flow determination. Time-averaged flow rates ($\bar{Q}$) through the artery were read out on a digital display. Both pulsatile flow and pressure tracings were recorded on an ultraviolet 6-channel recorder (S. E. Laboratories). At the end of each experimental run and occlusion zero sufficient time was allowed for hyperhaemic compensation. The stability of the preparations was excellent throughout the experiments, as evaluated by heart rate, systemic pressure and periodic unrestricted flow rate measurements.

Our constricting device consists of a 2-0 nylon suture looped through a very small ring, and held at each end by two blocks of plastic. The two plastic blocks are mounted on a pair of metal rods; one of the blocks is moveable, thereby altering the loop diameter. The distance between these blocks can be measured accurately with a vernier caliper, the relation between this distance and the corresponding decrease in radius of the loop being linear.

Arterial wall thickness was estimated at the end of the experiments on frozen and fixed tissue sections using a travelling microscope. A certain amount of error must have been incorporated by not taking into account the changes in wall thickness due to distending pressure (although the artery is distended against a constricting and unyielding loop) and due to the unavoidable tissue volume changes secondary to processing. Corrections for wall mass displacement which occur in the stenosed segment in the range of severe constrictions, were made on the curve representing internal radii by extrapolating the values of zero flow and maximal pressure gradient of those of zero internal area.

In order to study the effect of length of the stenosis on the energy loss of the blood flowing through it, we used split and bored plastic blocks of known length and contricting diameters. Accepting the Shippley and Gregg[10] demonstration, we assumed not significant wall mass displacement in the experiments carried out using plastic blocks as external constrictors.

Pressure data were obtained by averaging the reading of 15 cardiac cycles. Kinetic energy computations were made by differentiating the values of the velocity at very small time intervals and computing the kinetic energy for each one of these elements.* Plots of kinetic and lateral pressure energy were made in terms of a height of a water column (cm).

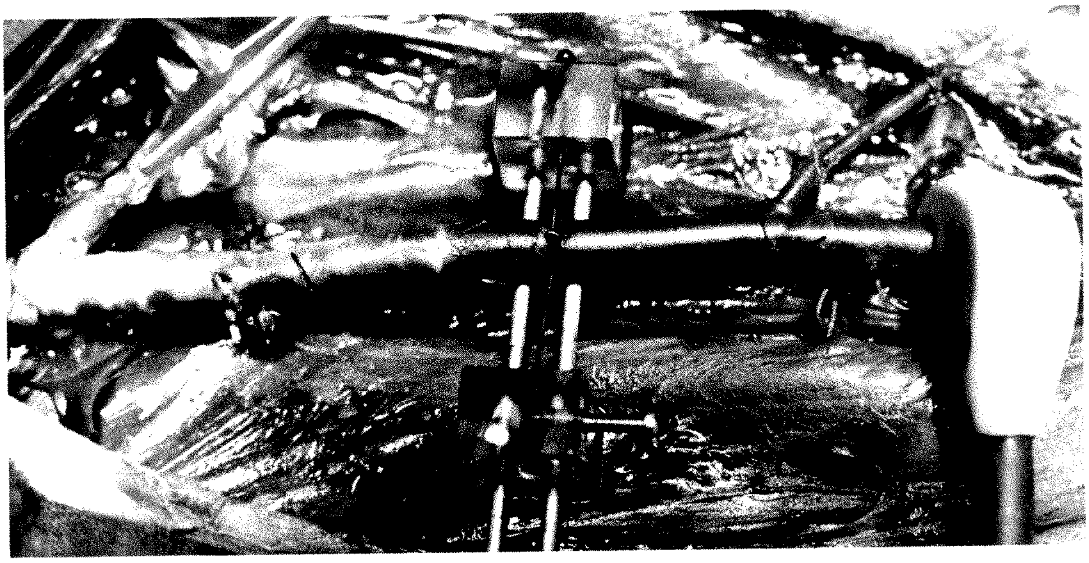

FIG. 5. Photograph of the experimental preparation showing the two side branches cannulated for pressure measurement, and the electromagnetic flow transducer *in situ*. The constricting loop is seen in the mid portion of the femoral artery.

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* See appendix.

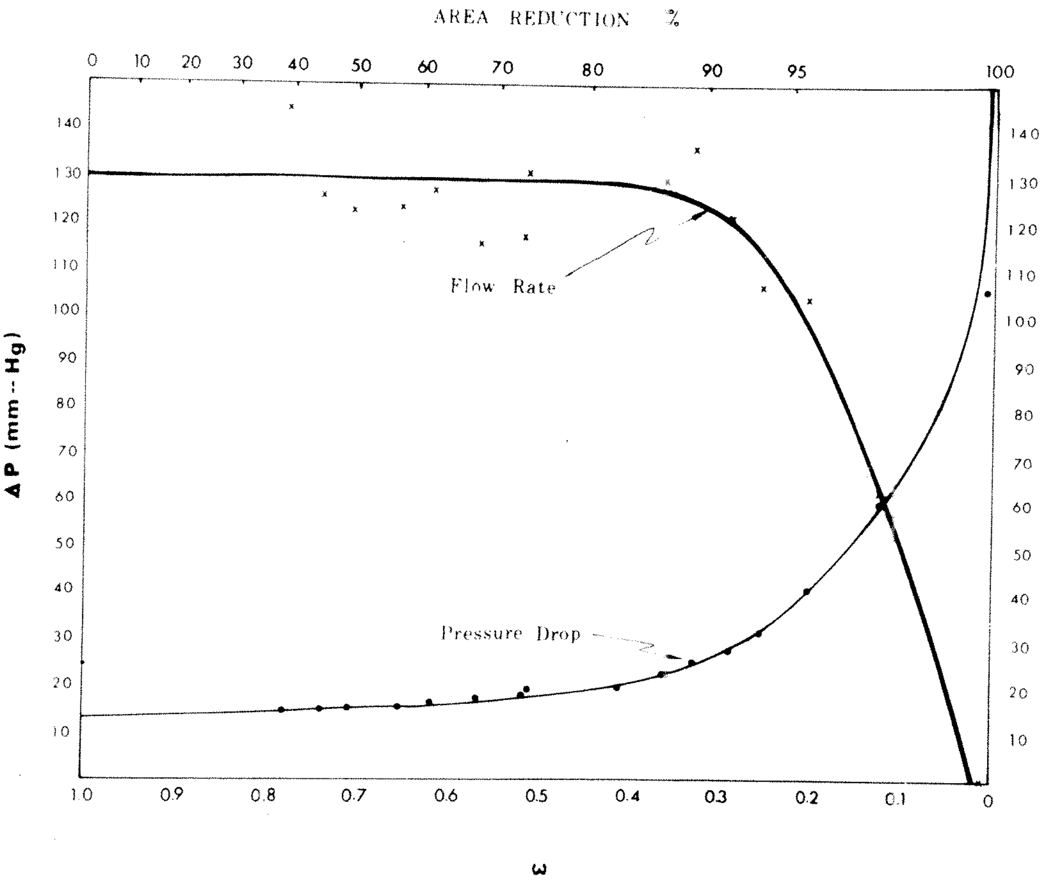

FIG. 6. Flow and pressure changes with increasing stenosis, plotted against radii ratio (ω). The scale showing percentage of stenosis is added to the top of the graph for comparative reference.

Results

A typical tracing of the flow and pressure changes with increasing stenosis (loop constrictor) is shown in Fig. 6. The scale showing percentage of occlusion is added to the ω scale for reference.

We had predicted that before reaching the critical range, the experimental values of Ek_s/Ek_1 would follow the theoretical curve. This close correlation can be seen in Fig. 7 which displays data measured in two experiments in the same animal against the theoretical curve. Within the critical range, the experimental values should be smaller and fall from the theoretical curve because, having incurred a drop in flow volume, hence a drop in V_1 and Ek_1, the value of Ek_s will be smaller since it is expressed as "n" times that of a smaller Ek_1.

In order to show this departure from the theoretical curve more clearly, we have plotted the latter against the experimental data in logarithmic scales (Fig. 8). The solid straight line with the 4 to 1 slope represents the theoretical fourth powered function (equation 5). The beginning of the critical area is clearly shown by the departure of the experimental data from the theoretical line. Beyond this point of departure, the velocity, and, hence Ek_s, continues to increase although it does so at a slower rate than before the critical point was reached. This increase can only continue for a very short distance (as indicated by AB in Fig. 8) until a point is reached where the velocity through the stenosis reaches a maximal value (Max) and then decreases. After this maximal point, the fall to zero flow is nearly instantaneous.

The stenotic values between th critical (departure)

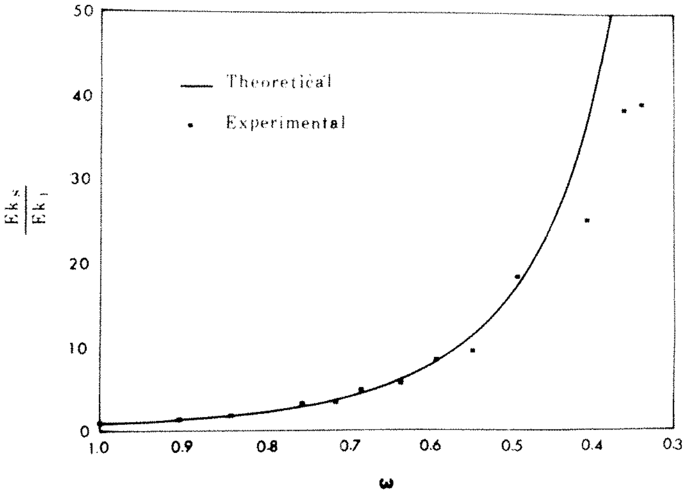

FIG. 7. Theoretical and experimental values of kinetic energy plotted against the ratio of radii (ω). Note the close correlation between theoretical and experimental values up to a value of $\omega = 0.45$.

point and the Max point could be termed the critical range. The departure point is that point beyond which pressure and flow decrements will occur with even the slightest additional constriction and is, therefore, the "critical" point.

Figure 9 shows the effect of increasing the length of two different stenotic segments on the flow rate in the femoral artery. Two series of drilled blocks (4 mm and 3 mm) were used which provided vessel lumen of 0.063 mm² and 0.0165 mm² respectively in this particular animal. The steeper curve for the 3 mm series correlates well with the theoretical prediction (Equation 8).

From the above derivations and data, it is clear that the "critical" value of a stenosis depends mainly on the velocity of the flow and on the area ratio (or radii ratio = ω) between the stenosed and unstenosed segments of the vessel. Changes in length and viscosity (within physiological limits) are less important in determining the critical value.

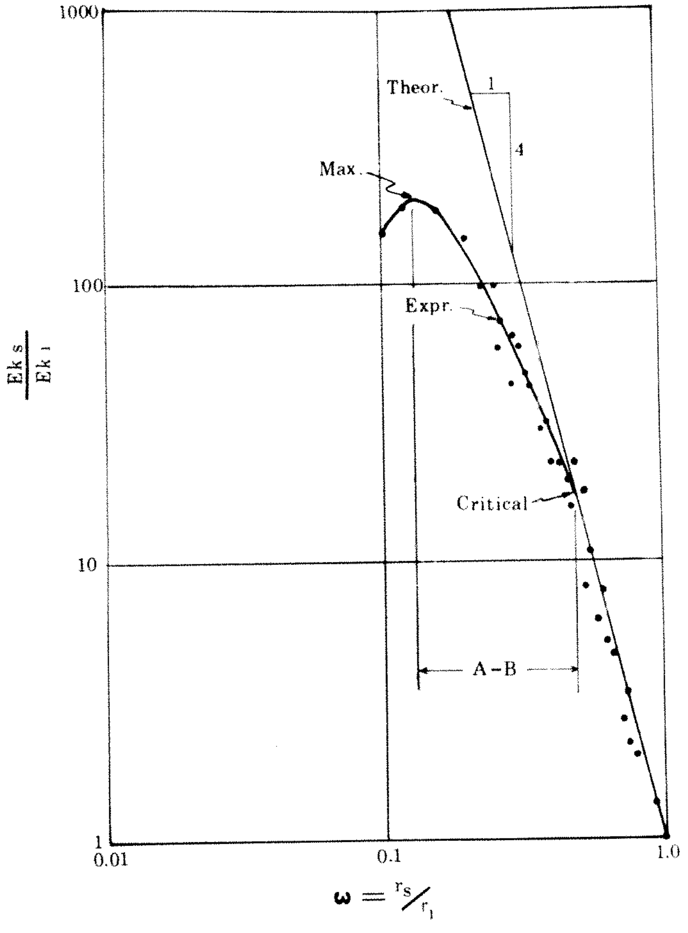

Fig. 8. Experimental data (Expr.) plotted with the theoretical function (Theor.) against the ratio of radii (ω) on log-log scales. The critical (departure) point and the point of maximal kinetic energy (max) are indicated. The critical range is designated (A-B).

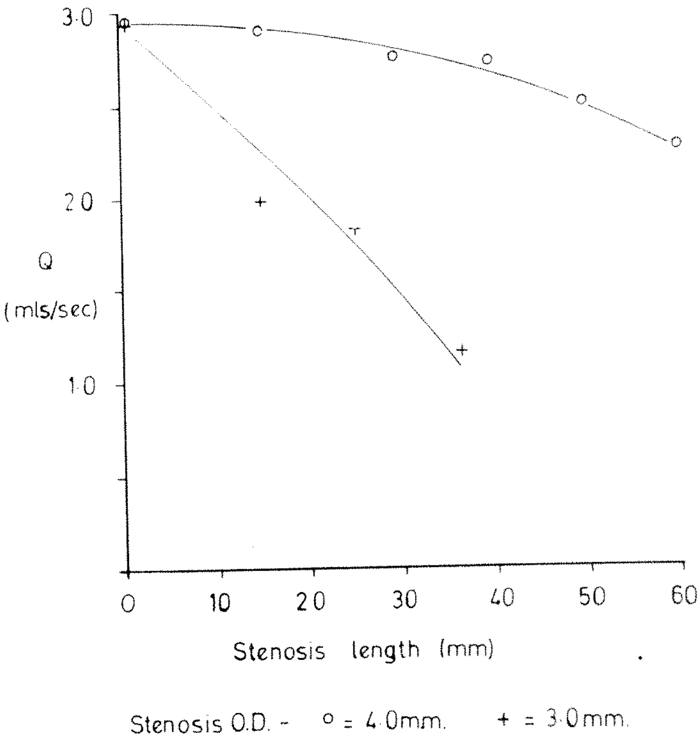

Fig. 9. Graph showing the effect of increasing the length of the stenosis on the flow rate. (o): Constricting block giving a vessel outside diameter of 4.0 mm; (+) idem. of 3.0 mm.

Discussion

Review of the Previous Experimental Models on Arterial Stenosis

The experimental work on the problem of arterial stenosis has been performed using mainly two types of models: physical and biological systems. Mathematical models have been infrequently used, probably because of the complexity involved in describing arterial blood flow in precise fluid dynamic terms. Although the Poiseuille equation has been extensively quoted, its inadequacy for predicting changes in flow or pressure secondary to stenosis has been the subject of some studies, such as those of Byar[2] and of Delin.[3] This fact should come as no surprise for the conditions implicit in the derivation of Poiseuille's equation make it non-applicable to the problem of localised stenosis.

Empirically derived formulas—such as the one presented by Byar[2]—throw little light on the subject in terms of providing either a tool or an understanding of the phenomenon under consideration.

May[8] introduced a mathematical model of a stenosis that, because of its apparent simplicity, is worthwhile discussing. Their model equation has three terms representing the pressure losses contributed by the stenosis, the contraction and the expansion of flow, respectively. The first term $(8\,\mu L/R_1^2)V_1(A_1/A_s)^2$ is derived from

Poiseuille's equation through a continuity proposition. It must, therefore, apply only where Poiseuille's equation does apply: pulsating flow through a localised constriction is not such a case. Their second term $(4.8\ \mu/R_1)\ V_1(A_1/A_s)^{1\ 1/2}$ is an empirical one and is obviously based in Poiseuille's equation as well. The third term of their model $\rho V_1^2(A_1/A_s)^2$ is somewhat puzzling. It is presented as being derived from the calculation of head loss in a pipe due to sudden expansion. Such loss in hydraulics has been quoted above (equation 6) as $(V_s - V_1)^2/2g$. By applying Bernoulli's principle through a mass-continuity proposition, this term can be easily transformed into the form of $(\rho/2)V_1^2(A_1/A_s - 1)^2$ which although different does have a certain similarity with that of the third term used by May.[8] However, even if this term were the same as the one that they used, it must be borne in mind that this hydraulic formula has been experimentally derived and applies only to turbulent flow. It is hardly acceptable to introduce into a 3-term equation two terms applicable to laminar flow (Poiseuille) and a third one which is only applicable to turbulent flow and whose derivation is not clear. We agree however, with their conclusions regarding the important factors that determine the value of the critical area of a vessel.

Among the physical models, the most often used are either a constant head of pressure (gravity flow) or a rotary pulsatile system. Mann's[7] original experiments involved both types of systems. His results are clear evidence that the two systems are not comparable, and this should be borne in mind when making deductions to be applied to animal or human arteries.

The animal models have generally been complementary to physical models. They reproduce in a more realistic way what happens in the human arteries, but they have the usual drawbacks of lacking the steadiness of a physical system and of incorporating variables that change the parameters under investigation (autoregulation, etc). In spite of this, they are the ultimate test of any arterial haemodynamic problem before inferences are made which are applicable to human arteries. Some of the drawbacks in the use of physical and animal models are discussed in the next two headings.

The Calculation of the Area of Stenosis Caused by a Constriction

Much of the work on critical stenosis has been done using external constrictions imposed on an artery. From the known values of the external constriction, the value of the internal lumen is derived. When this is done in arteries, whether interposed in a physical model or "in situ," the calculation of this inside lumen implies some assumptions.

Mann,[7] assumed that the percentage of external constriction of a vessel would be directly proportional to the percentage of internal constriction. Assuming the wall thickness to be constant is a source of serious error, as was pointed out by Shipley and Gregg.[10] They showed that with Mann's assumption, the total occlusion of the vessel would occur earlier than would be expected from calculations. Shippley and Gregg convincingly argued that with the constricting blocks they used (10 mm) there was no mass extrusion and, therefore, the internal lumen can be predicted from the values of external diameter and the assumption of constant wall mass. These conclusions apply to constricting blocks of over a certain length but do not apply to tight, minimal-length stenoses, such as those produced by a fine thread around an artery.

In those of our experiments that were performed using constricting blocks (minimum length 10 mm) the assumption of a constant wall volume was made. In the experiments using the nylon loop the curve that defined the internal radius for progressive constrictions was extrapolated to the point where flow rate is zero and the pressure drop reaches its maximum value to correct for the wall mass shift in the constricted vessel.

Some workers[3] have used radiographic measurements of the stenotic areas. The precision of this technique at high values of stenosis does not seem beyond question, even when 2 plane projections are used.

Resistance to Flow

The establishment of a "fixed" peripheral resistance in flow models has been the source of some interpretative errors. Most of the physical models used in previous work[2,4,7,10] have achieved a "fixed peripheral resistance" by placing a small bore tube or a screw-clamp at the distal end of the circuit. It must be said beforehand that one cannot "fix" the peripheral resistance by simply placing an obstruction at the end of a tube while varying either Q or P. For if Q is kept constant, varying P by ΔP would result in a variation of the resistance, ΔR

$$\frac{P + \Delta P}{Q} = R + \Delta R$$

Similarly, if P is kept constant, varying Q by ΔQ would also result in a change in resistance, ΔR′,

$$\frac{P}{Q + \Delta Q} = R + \Delta R'$$

To place a "high peripheral resisistance" at the distal end of the tubing is basically creating a second critical stenosis downstream. The result of this second critical stenosis is to decrease Q_1 and hence V_1. This decrease in velocity in the pre-stenotic segment under study will result in a much narrower stenosis being now needed to achieve the "critical" constriction.

This is the flaw in Fiddian's work which led him to conclude that the area ratio between unstenosed and stenosed areas would not influence the value of the critical area. By placing a "high peripheral resistance" in the three different diameters of tubing which he used to simulate the sizes of human aorta, dog's aorta and dog's femoral artery in his experiments, he concluded that the critical stenosis area was about 2.3 mm^2 for all three systems. However, if we use his data to calculate the respective mean velocities, we shall find them to be approximately 1.8 cm per second for the human aorta model, 8.4 cm per second for the dog aorta, and 57 cm per second for the dog femoral model. The actual mean velocity in the human aorta is about 20 times higher. His model, therefore, did not represent the conditions that he was trying to simulate. In fact, under a mean pressure of 100 mm Hg his flow data shows that for both the aortic models, and specially for the human, the peripheral resistance in his model acts as a critical stenosis as shown by the very slow velocity in the tubes.

The Different Families of Flow and Pressure Curves in Progressive Stenosis

Previous research in this field of arterial stenosis[4,8,10,12,13] has shown that when plotting stenotic areas versus flow rate (or pressure values distal to the stenosis) the resulting curves have different shapes and give different values for critical areas for the same vessel, depending on whether it is a high or a low flow rate situation. Thus, with progressive constrictions in a high flow rate system, the critical stenosis appears sooner and the curve representing the fall in flow rate (or in post-stenotic pressure) has a smaller slope than in a low flow rate system. In the latter, the critical point appears later and the fall in flow rate (or in pressure) is more precipitous beyond the critical point. This is illustrated in Fig. 10.

We have seen that the gain in kinetic energy (Ek_s) through the stenosis is at the expense of the lateral pressure energy (Ep_s), and that this gained kinetic energy is mostly lost in the post-stenotic segment. Thus, the curve representing the gain in kinetic energy through the stenosis is nearly the same as the curve representing the drop in lateral pressure energy (Ep_2) in the post-stenotic segment. There is a small difference between both curves accounted for by the energy lost in contracting the flow at the inlet and the friction loss at the stenosis. We will now show how the function $Ek_s/Ek_1 = \omega^{-1}$ can explain these different families of curves for different flow velocity systems.

In an arterial segment, providing we are dealing with stable experimental conditions, the total energy per unit weight (Et) contained in the blood which flows through a cross-section is constant. The kinetic (Ek) and the lateral pressure (Ep) components, can be expressed as percent fractions of the total energy (Fig. 11). In a high flow condition (h) such as exercise, arteriovenous shunting, etc., the amount of energy allocated to the kinetic component—$Ek_1(h)$—will be a substantial proportion of the total energy available. Let us give a high

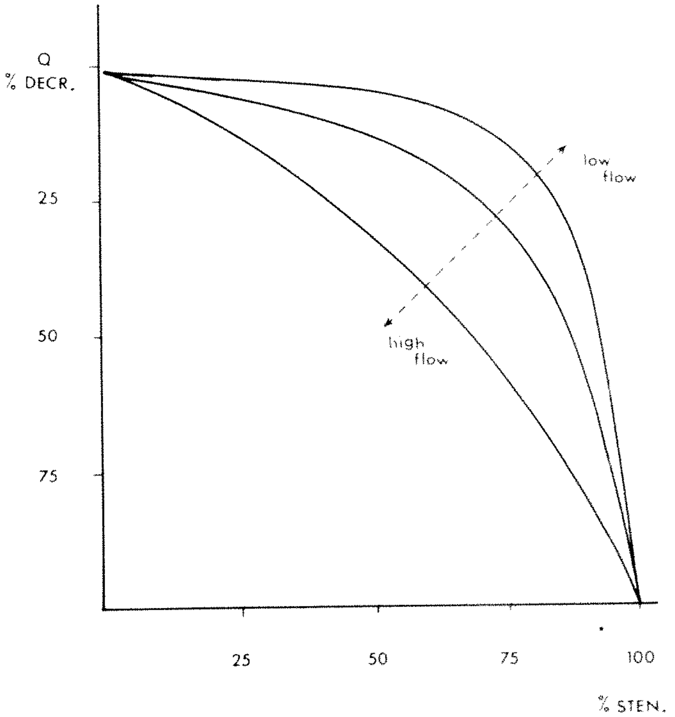

FIG. 10. Graph of percentage decrease in flow obtained for progressive stenosis under high, medium and low flow conditions.

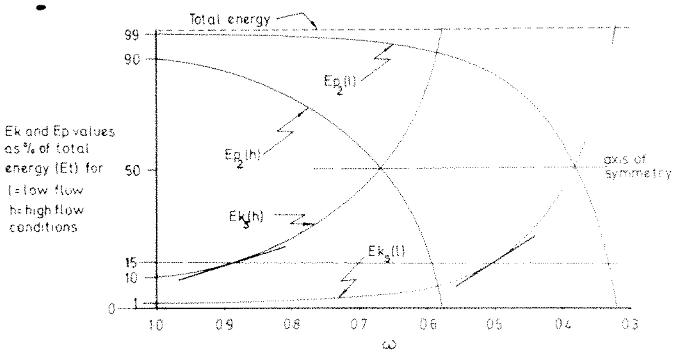

FIG. 11. Graph showing changes in the lateral pressure (Ep) and kinetic (Ek) components of the total energy in a vessel for different degrees of stenosis, considering kinetic energy at the stenosis (Ek_s) and lateral pressure energy in the post-stenotic segment (although for practical purposes $Ep_s = Ep_2$). Two cases are considered: a high flow condition (h) with the kinetic component being 10% of the total energy, prior to any stenosis ($\omega = 1$), and a low flow condition (l) with the kinetic component representing 1% of the total energy at $\omega = 1$. The 15% level of total energy has been marked and is considered to be within the critical range.

value, say 10% of the total energy, to $Ek_1(h)$ in the curve representing the function $Ek_s(h)/Ek_1(h)$, for a progressive decrease of the lumen area ($\omega \rightarrow 0$), the function $Ek_s(h)/Ek_1(h)$ will rapidly approach the level of 15% of the total energy. This rise will be reflected by a similar (and detectable) drop in lateral pressure energy as shown in Fig. 11 by $Ep_2(h)$. One may notice the similarity between the graph of this drop and that depicted as typical of high flow conditions (Fig. 10 high flow curve).

Conversely, the percentage of total energy allocated to the kinetic component in a low flow situation—$Ek_1(1)$—is a small fraction, generally less than 1%. Thus, it requires a much higher degree of stenosis for the function $Ek_s(1)/Ek_1(1)$ to approach a value of 15% of the total energy, and hence to show a measurable drop in lateral pressure energy—$Ep_2(1)$—than is required in the high flow condition to obtain the same result. When this value (15%) is approached, that is when the stenosis is within the critical area, we are dealing with that portion of the function ω^{-4} that has a very steep slope (Fig. 11). If we consider that, beyond the stenosis, the changes in kinetic energy are approximately inversely proportional to the changes in lateral pressure energy, we can see that, in a low flow condition, the changes observed within the critical area occur at a faster rate than in a high flow condition.

In an experimental situation, a 15% drop in the lateral pressure energy is definitely a measurable change. When this occurs across a stenosis, we can assume that the critical range has been entered. The drop in lateral pressure energy (post-stenotic) being proportional to the gain in kinetic energy through the stenosis, we shall arbitrarily set this value of 15% as one which is definitely within the critical range, in order to discuss the behaviour of the function that describes energy changes through a stenosis. This is not to say that 15% is what we define as a critical stenosis but is a deliberately chosen value which we know must be within the critical range.

Conclusions

Although the mechanics of blood flow through a stenosis is known to be a dynamic problem, its interpretation as a static, purely geometrical problem has been used in both research and clinical work. Thus some authors have defined the "critical" narrowing of a vessel in terms of the area ratio between the stenosed and unstenosed portions.

On the other hand, experimental results have led others to conclude that the "critical" area of a stenosis depends on the peripheral resistance and on the actual area of the stenosis while the area of the unstenosed segment of the vessel would bear no relation to the value of the "critical" area of stenosis.

By considering the mechanics of the blood flow through an arterial stenosis from the standpoint of energy transfers, we have attempted to provide a physical grasp of the fluid dynamics involved, which could be used as a tool in evaluating arterial lesions in man. Our experimental results correlate well with the theoretical solution. In the calculation of the values, the assumption of a flat velocity profile was made. The possible magnitude of error involved with this assumption is discussed in the appendix. The changes induced in the system by the elastic properties of the arterial wall are not incorporated in the computation as their relative magnitude is not thought to be of importance. For the size of artery of our interest, the role of viscosity has been studied by other workers[2] and follows the simple Newtonian law. The importance of the length factor as seen in the experimental data, correlates well with the theoretical expectations. The most important factors in determining the "critical" value for the stenosis of a vessel are the flow rate in the unstenosed vessel and the ratio of areas between the stenosed and unstenosed segments.

The development of a pressure gradient or the decrease in volume flow secondary to a critical stenosis is a reflection of energy loss through it. Most of this loss occurs through the conversion of lateral pressure energy into kinetic energy, the subsequent loss of the latter being mostly irretrievable as it is spent in the generation of jet turbulence in the post-stenotic segment. The critical area is defined, for each particular flow rate, as the area ratio where the values of the kinetic energy through the stenosis deviate from the theoretical curve. The critical range of a stenosis is defined as the range of values between the critical area value and that where the velocity reaches its maximum value.

The influence of the peripheral resistance on the values for critical stenosis is affected through the changes that it produces in flow velocity (V_1).

The geometrical ratio between stenosed and pre-stenotic segments and the velocity in the pre-stenotic segment provide sufficient information to anticipate the approximate value of a critical stenosis if the total energy of the system is known. In most large and medium sized arteries, the value of the lateral pressure energy at rest (in the horizontal position) approximates to the total energy value in the vessel, kinetic energy being a small fraction of the latter. Under conditions of high flow rates (exercise, drug-induced vasodilation, arterio-venous communication) the kinetic energy component becomes important and must be taken into account. Measurement of pressure gradients across stenosis under operative conditions (low cardiac output, increased peripheral resistance; hence, low velocity, etc) does not provide an answer to the significance of a lesion. Vasodilating drugs may be used to induce high volume flows, although the magnitude of this increase may not correspond to that obtained by exercise.

Appendix

In most fluid systems, velocity distributions over a cross-section are quite pronounced. This variation in velocity, plus the fact that kinetic energy is a power function of velocity, can introduce errors in the computation of kinetic energy when using the space-average value of velocity, that is, assuming the velocity profile to be flat.

A similar type of consideration has to be made with respect to the time-average velocity, when dealing with any type of time dependent flow, such as pulsatile arterial flow. In the same manner, the use of time-averaged values of velocity can introduce considerable errors in the computation of kinetic energy values.

Errors Introduced by the Assumption of a Flat Velocity Profile

Considering steady flow, the weight of the fluid that passes through a cross section of the vessel in unit time equals γQ; Q: discharge, γ (specific weight) $= \rho g$.

The true average kinetic energy over the cross-section of the vessel, expressed in K.E. per unit weight would be:

$$\frac{1}{2gQ}\int_A v_{(s)}^3\,dA \qquad [9]$$

Comparing equation 9 with the conventional way of computing kinetic energy:

$$V^2/2g \qquad [10]$$

we have:

$$\frac{\frac{1}{2gQ}\int_A v_{(s)}^3\,dA}{V^2/2g} = \frac{\frac{1}{2gQ}\int_A v_{(s)}^3\,dA}{V^3A/2gQ} = \frac{\int_A v_{(s)}^3\,dA}{V^3A} = \alpha \qquad [11]$$

This ratio (α) between the true value of the kinetic energy and the value of the kinetic energy computed by using the average velocity $v = Q/A$ is called the "coefficient of kinetic energy." This coefficient will be larger than 1.0 unless the velocity is uniform across the entire cross-section. In steady laminar flow (parabolic distribution) the value of $\alpha = 2.00$, while for turbulent flow in a smooth pipe $\alpha = 1.06$. Hence, the error involved in using the space-average value of the velocity in the term $v^2/2g$ for computation of kinetic energy amounts to 6% in fully developed turbulent flow and to 200% in laminar flow.

Error Introduced by Using the Time-averaged Value of Velocity ($\bar{V}$) for the Computation of Kinetic Energy

Assuming now a flat flow profile, the true time-average of velocity in unsteady flow is:

$$\bar{V} = \frac{1}{T}\int_T v_{(t)}\,dt$$

T being the time period over which the average is taken. We have then,

$$Ek = \frac{\bar{V}^2}{2g} = \frac{\left[\frac{1}{T}\int_T v_{(t)}\,dt\right]^2}{2g} \qquad [12]$$

The true average kinetic energy can be calculated from the velocity recordings (as functions of time) by considering small increments of time (dt) when the instantaneous velocity is $v_{(t)}$. The volume of fluid that passes through the vessel cross-section in this period (dt) is $Q = Av_t\,dt$ and its weight: $\gamma Av_{(t)}\,dt$

Kinetic energy per unit weight in this time period will be $v_t^2/2g$ and the kinetic energy of the total fluid weight passing through the cross-section will be:

$$\frac{v_{(t)}^2}{2g}(\gamma Av_{(t)}\,dt) = \frac{\rho}{2}Av_{(t)}^3\,dt$$

which over a long period of time (T) will equal:

$$\frac{\rho}{2}\int_T Av_{(t)}^3\,dt \qquad [13]$$

The time averaging Ek per unit weight will be:

$$\frac{\frac{\rho}{2}\int_T Av_{(t)}^3\,dt}{\gamma\int_T Av_{(t)}\,dt} = \frac{1}{2g}\frac{\int_T v_{(t)}^3\,dt}{\int_T v_{(t)}\,dt} \qquad [14]$$

comparing the values from equations [14] and [12]:

$$\frac{\frac{1}{2g}\frac{\int_T v_{(t)}^3\,dt}{\int_T v_{(t)}\,dt}}{\frac{1}{2gT^2}\left[\int_T v_{(t)}\,dt\right]^2} = \frac{\int_T v_{(t)}^3\,dt}{\frac{1}{T^2}\left[\int_T v_{(t)}\,dt\right]^3} = \alpha_{(t)} \qquad [15]$$

We shall call $\alpha_{(t)}$ the "time coefficient of kinetic energy." Its value depends entirely on the waveform.

Considering arterial blood flow, the errors involved in computing kinetic energy values by using its time-averaged velocities ($\bar{V}$) are greater than those involved in using the space-averaged velocities ($\bar{V}$). In space-averaged velocities, the largest possible error in computing kinetic energy values would be in the case of a parbolic flow profile (laminar) when the true kinetic energy value would be 200% higher than the estimated assuming the same average velocity for the entire cross-section. It is doubtful that a true parabolic profile ever exists in arterial blood flow and, if it does, it could only occur in certain locations and for a short period in each cardiac cycle.

The errors involved in using time-averaged velocities for the computation of kinetic energy values are of greater magnitude. In certain physiological waveforms we have found the true values of kinetic energy to be over 1,000% higher than those obtained by computing kinetic energy from recorded time-averaged velocities.

In this study we have computed the kinetic energy values from differential time elements in the waveform according to equation (14). We have assumed a flat velocity profile. The reason for this lies in the difficulty of plotting the flow profile through the stenosis and in the fact that, as the stenotic area decreases, we are dealing with a turbulent jet in which the coefficient of kinetic energy must approach the 1.06 value.*

In fact, in the range of very small areas of stenosis, the errors incurred in the computation of kinetic energy depend more on the difficulty of estimating with accuracy the cross-sectional area of the vessel, than in time or space velocity distributions, for the flow becomes a turbulent jet (flat profile), and the velocity wave is damped and approaches the configuration of the time-averaged velocity tracing.

In detailed haemodynamic studies, it may be necessary to consider both the space and time distributions of velocities simultaneously. The basic mechanics are provided in equations (1 and 15), and the computations provided in equations (11 and 15), and the computations space (A) and time (T).

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* The errors incurred by computing kinetic energy values from time-averaged velocity values also become smaller as the stenotic area decreases because of the damping effect of the velocity wave amplitude. These are still of sufficient magnitude to be unacceptable for computation of kinetic energy values.

The Fine Structure of Experimentally Induced Connective Tissue Complexes in the Human

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The growth, development and cellular activity of fibrocollagenous tissue complexes induced by the implantation of specially structured wire mesh cylinders in 22 human male volunteers were studied during the time course of fibroplasia utilizing light and electron microscopic techniques. The fibrocollagenous tissue complexes after 4 to 16 weeks of development demonstrated highly ordered lamellations made of zones consisting primarily of fibroblasts and zones consisting primarily of collagenous fibers. The development of the ordered lamellations is referable to specific fibrillogenic activities by the constituent fibroblasts. The initial role of the fibroblast in fibrillogenesis is indicative of an apocrine-like secretory process followed by a holocrine-like role which results in cytodestruction and concurrent formation of an avascular collagenic tissue referable to an organizing cicatrix in a healing wound.

THE LITERATURE contains many ultrastructural studies on laboratory animals concerning inflammation and wound repair. In regard to comparable studies of wound repair in man, little information has been available. Hartwell's observations[20] have suggested certain healing differences between man and laboratory animals. Ultrastructural studies on human wound repair by Ross and Odland[64] and Odland and Ross[43] were felt to compare favorably with previous studies on guinea pigs and rats.

Experimental models used to study connective tissue involvement in animal wound healing has included inducement by direct incision,[23,60–62,64,65] by tissue culture methods,[1,27,51] and induction by formation of the carrageenin granuloma.[24,36]

One method of experimental investigation involves the implantation of specially structured mechanical devices. These devices provide a sterile dead space which serves as: 1) an inducer of the connective tissue regeneration phase of the healing wound; and 2) a substrate for the developing connective tissue complex. Some of the devices used include polyvinyl sponges,[5,9,42,67] perforated celluloid spheres and methacrylate cylinders,[17] knitted Dacron cylinders,[12,44] and stainless steel and tantalum wire mesh spheres or cylinders.[56,58,65,66,69,79,80]

The use of the mechanical devices has the advantage of producing standardized, highly ordered, fibrocollagenous tissue complexes without the interference of epithelization. Further, the separation and characterization of certain cellular and fluid components of the regenerating connective tissue for biochemical, physiological, and morphological studies has been made possible by the use of mechanical devices. Because of its unique versatility, the stainless steel wire mesh cylinder has been chosen as the model for this study.

Previous studies have utilized stainless steel wire mesh cylinders implanted in experimental dogs for the purposes of studying blood and lymph vascular components,[67,68] blood and wound fluid,[34,56,79,80] extravascular fibrocollagenous tissue components,[54,55,58,59,67,68] and the morphologic structure of the tropocollagen molecule.[57–59]

The purpose of this study is to: 1) morphologically characterize fibrocollagenous tissue complexes structured *in vivo* in human male volunteers with reference to changes during the time course of fibroplasia; 2) investigate the fine structural aspects of the extravascular tissue complexes which bear on the problem of collagenic fibrillogenesis; and 3) analyze and compare the findings with previously reported morphological data related to experimentally induced fibrocollagenous tissue in animals.

Methods and Materials

Fibrocollagenous tissue complexes were induced in a group of 22 human male volunteers who had received

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prior physical examinations to determine their state of health and suitability for implantations of specially structured stainless steel wire mesh cylinders. Induction of the fibrocollagenous tissue complexes followed procedures previously described by Schilling *et al.*,[67] and Richter and Schilling.[58] The steel mesh cylinders (7.2 to 7.6 cm long by 1 cm in diameter with closed ends) were fabricated from mesh no. 40, surgical foundation wire mesh.

Using local anesthesia and aseptic conditions, two cylinders were implanted in the superficial fascia of the upper abdominal quadrants. The inducing cylinders were reclaimed at intervals of 2, 3, 4, 8, 12, and 16 weeks. Upon reclamation, the cylinders were opened longitudinally and immediately immersed in the appropriate fixatives for light or electron microscopic studies. The tissue was dissected away from the steel mesh during the first few minutes of fixation.

The collagenous tissue complexes for light microscopy were fixed in a 10% neutral buffered formalin solution (pH 7.0), washed, dehydrated and embedded in paraffin. The stains employed were Harris' hematoxylin-eosin, periodic acid-Schiff, Gomori's reticular stain and Van Gieson's picrofuchsin.[2] Additional stains included Heidenhain's "Azan"[35] and elastica.[32] The sections were examined with an AO Spencer and a Wild M20 research microscope.

A 12-week-old tissue complex was cleared of paraffin with xylene, dehydrated, placed in a 1% aqueous osmium tetroxide solution for three weeks and sectioned freehand in a transverse plane. The gross structure of the tissue complex was studied with an AO Spencer dissection microscope.

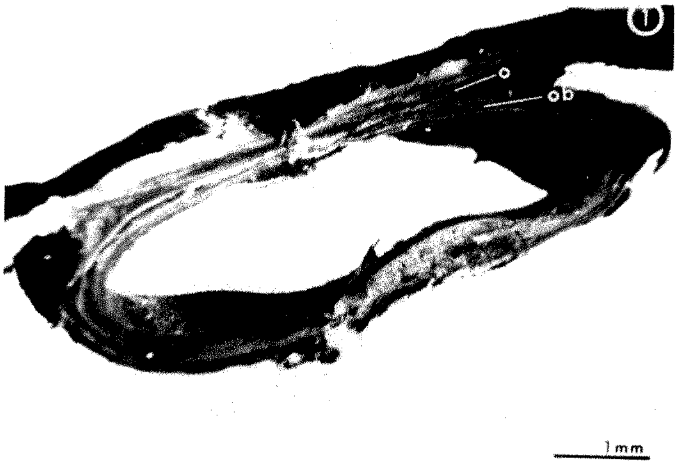
The tissue complexes for electron microscopic study were immediately immersed in cold fixative (5 C), dissected from the steel mesh and minced into 1 mm square pieces. The fixative and fixation time exployed was either a 1% osmium tetroxide solution buffered with Sorenson's phosphate buffer (pH 7.4) for 2 hours, or a 6.25% gluteraldehyde buffered to pH 7.4 with s-collidine for 2 hours and post-fixed with 1% aqueous osmium tetroxide for 1 hour. The tissue was washed, dehydrated in ethyl alcohol, and infiltrated with a methacrylate mixture (25% n-ethyl-and 75% n-butyl-methacrylate). The infiltrated tissue was placed in Beem capsules and polymerized with U-V light. Ultrathin sections were cut with a Porter-Blum MT-1 microtome, and mounted on formvar coated specimen screens.

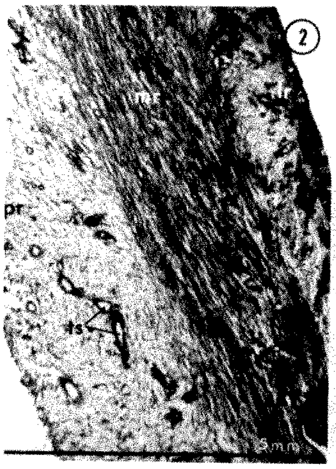
While various stain combinations were investigated, a 1% aqueous uranyl acetate solution (staining time 5 minutes in a 60 C oven) used in conjunction with lead citrate[75] proved very satisfactory. A 1% phosphotungstic acid solution was used to stain collagen; however, the general contrast was not as satisfactory in the human tissues as in previously studied animal tissues treated in the same experimental manner. The ultrathin sections were examined with an RCA EMU-4A electron microscope.

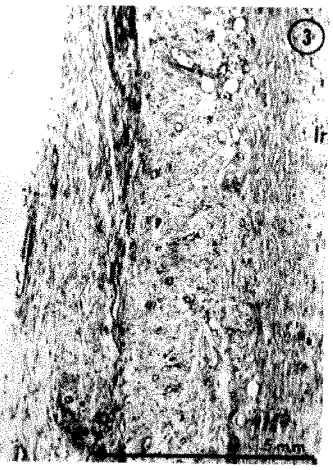
Observations

Gross and Light Microscopic Observations

When the wire mesh cylinders were retrieved and the connective tissue complexes dissected from the mesh, they reflected the long cylindrical shape and size of the induction device. In cross sections, older (4 through 16 weeks) osmicated tissue complexes exhibited concentric osmiophilic cellular and osmiophobic fibrous zones which impart a lamellated appearance to the complex (Fig. 1).







FIGS. 1–3. FIG. 1. A 12-week-old osmicated fibrocollagenous tissue complex cut free-hand in a transverse plane exhibits cylindrical conformity to the induction device. The osmiophilic (o) and osmiophobic (ob) zones impart a lamellated appearance to the tissue complex. (Stained with osmium tetroxide, × 22.8). FIG. 2. By 4 weeks of development, the fibrocollagenous tissue complex has developed a luminal region (lr), a mid-region (mr), and a peripheral region (pr). The peripheral region exhibits cell-lined tissue fluid spaces (ts). (Gomori's reticulum stain, ×159.6). FIG. 3. A 12-week-old tissue complex demonstrates the cellular character of the luminal region (lr). One fibrous zone (fz) is readily apparent, a second is developing adjacent to the luminal region. (Stained with Heidenhain's "Azan," ×111.6).

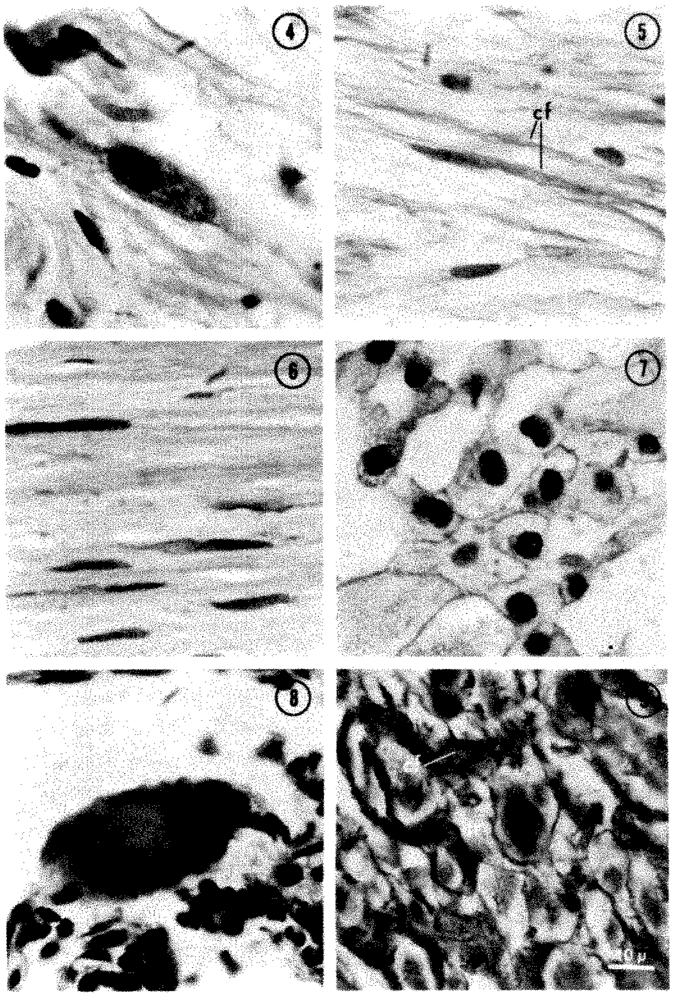
The tissue complexes after 12 to 16 weeks of growth have a measurable wall thickness of 0.8 mm to 1.5 mm. During the removal of the induction devices it was noted that the tissue immediately surrounding the induction device was highly vascularized.

The primary cell type identified in the tissue complexes is the fibroblast. The 2-week-old tissue complexes are primarily cellular with a minor amount of fibrous material present. The fibroblasts around the lumen in cross-sectional profile appear as long attenuated polar cells with the long axis of the cell parallel with the lumen. The cells around the lumen of all ages of tissue complexes (2 through 16 weeks) are descriptively the same and thus establish what may be termed a *luminal region* (Figs. 2 and 3). The fibroblasts more peripherally located are ovoid with branching cell processes. These cells exhibit no apparent orientation in relation to the induction device surface or the lumen. The peripherally located fibroblasts (Fig. 4) of the older tissue complexes (3 through 16 weeks) are descriptively the same and establish a *peripheral region* (Fig. 2). The fibrous material present in this region has a random interwoven appearance and exists mainly around the periphery of the cells.

The 3-week-old tissue complexes are predominantly cellular with luminal and peripheral region characteristics as previously described; however, in the midregion of the tissue (between the periphery and the lumen) a cylindrical zone of multidirectional fibers in which the long axis of the fibers course parallel to the lumen has developed. By the fourth week of growth more than one fibrous zone has developed and the fibrous zones are more discretely organized. These zones do contain fibroblasts which are widely spaced due to the amount of fibrillar material between them (Figs. 5 and 6).

Between the fibrous zones, cellular zones exist in which the cells are closely packed with a minor amount of fibrillar material deposited between them. This pattern of alternating fibrous and cellular zones can be collectively designated as a *midregion* (Fig. 2). The 8, 12, and 16-week-old tissue complexes are arranged essentially like the 4-week-old complex with the exception of having more fibrous zones developed in successively older tissue complexes (compare Fig. 1 to Fig. 2). As more fibrous zones are developed with age, the cellular peripheral region of the tissue complexes diminishes in width. Further, in the midregion the wider fibrous zones are more peripherally located with a diminution of the measurable width of the fibrous zones which are successively closer to the lumen (Fig. 1).

Using cytoplasmic basophilia as an index of the ribosomal content of the fibroblast, the fibroblasts of the peripheral region and some of the fibroblasts in the cellular zones in the midregion exhibited a strong basophilic cytoplasm. The cells of the fibrous zones, some of the fibroblasts of the cellular zones in the midregion and the fibroblasts of the luminal region had a decreased cytoplasmic basophilia as exhibited by a grayish colored cytoplasm.



Figs. 4–9. Fig. 4. A healthy, active fibroblast of the peripheral region adjacent to a fibrous zone of a 16-week-old tissue complex has demonstrable collagen fibers associated with the cell surface. (Stained with hematoxylin and eosin). Fig. 5. A fibroblast of a 4-week-old tissue complex fibrous zone has a long attenuated configuration. The collagen fibers (cf) appear to blend with the scanty cell cytoplasm. The collagen fibers range from very fine filamentous fibers to approximately 2.8 microns in diameter. (Stained with hematoxylin and eosin). Fig. 6. The nuclear configuration of fibroblasts in a fibrous zone ranges from long spindle-shaped nuclei with multiple nucleoli to remnants and fragments of cells undergoing cytodestruction. The tissue complex is 16-weeks-old. (stained with hematoxylin and eosin). Fig. 7. Foamy histiocytes were observed in the peripheral region of a 16-week-old tissue complex. These cells were generally found in clusters rather than occurring as single cells. (Stained with hematoxylin and eosin). Fig. 8. A foreign body giant cell observed in the peripheral region of a 3-week-old tissue complex is indicative of the type observed in other tissue complexes. Fig. 9. A reticulum stain demonstrates argyrophilic fibers (ar) blending with or in close apposition to the cell surface. The differentiated collagen fibers (cf) did not exhibit argyrophilia. (Stained with Gomori's reticulum stain). (Magnification of all figures is ×1206).

In determining the fibrous component of the tissue complexes, the elastic tissue stain was negative in all ages of development. Based on other stains used (Van Gieson's picrofuchsin, Heidenhain's "Azan," and hematoxylin-eosin) the fibrillar material was found to be collagenic. The reticular stain was positive (Fig. 9) and small argyrophilic fibers were observed around the peripheral margins of the fibroblasts.

The periodic acid-Schiff stain applied to the human connective tissue complexes was negative. Throughout the course of study, mitotic figures were not observed in any region of the tissue complexes.

Other cell types observed in the connective tissue complexes included eosinophiles, lymphocytes, "foamy" histiocytes and foreign body giant cells (Figs. 7 and 8). These additional cell types were generally located near the stainless steel mesh and were sparsely distributed. In the 3 through 16-week-old tissue complexes cell-lined tissue spaces were observed primarily in the cellular areas.(Figs. 2 and 3). The luminal areas of these spaces were unoccupied by cells or cell products.

Electron Microscopic Observations

The predominantly cellular areas of the tissue complexes are found to be comprised mainly of healthy fibroblasts (Fig. 10) with a minor amount of fibrillar material between the cells. The predominantly fibrous zones are comprised mainly of collagenic fibrous material with a few widely spaced cells and cell remnants in various stages of cytodestruction (Fig. 11).

The fibroblasts in the predominantly cellular areas (peripheral region and alternating cellular zones), display a wide spectrum of structural features. The endoplasmic reticulum may consist of granule studded membranes encompassing large dilated cisternae (Fig. 10) or smaller well-developed tubular cisternae which occupy a major portion of the cytoplasm (Figure 12). The ribosomes may be attached to form the rough endoplasmic reticulum or exist free in the cytoplasm.

The cytoplasmic matrix or hyaloplasm is of variable density. It may occur as a homogeneous matrix which is relatively electron-lucent or it may consist of localized electron-dense condensations in the cortical regions of the cell adjacent to the plasm membrane (Figs. 12 and 13).

The cytoplasm contains a fine filamentous or fibrous network (Fig. 13) distributed throughout the cytoplasm forming a cytoskeleton. These filamentous fibers measure from 50 Å to 90 Å in diameter. Condensations of these cytoskeletal fibers were observed in the cortical regions of the cell and in areas of the membraneous structures of the cell such as the nuclear membrane, the plasma membrane or the endoplasmic reticulum where they appear to blend with or form a part of membranes.

The formation of collagenic fibrils was observed in relation to a spectrum of changes occurring at or near the surface of fibroblasts comprising the predominantly cellular areas, particularly those of the alternating cellular zones. The various changes observed may occur simultaneously within localized areas of the individual cell. For purposes of description, the cyclic changes are divided into four phases. The designation of these phases (a_1 through a_4) have been previously used by Richter and Schilling[53] and will be used here in order to remain consistent with previous literature.

In the first phase (a_1) the plasma membrane appears as a normal intact structure. The cortical hyaloplasm is of minimal thickness and the fibrils of the cytoskeleton are randomly dispersed (Fig. 12).

The second phase (a_2) is denoted by the accumulation of an electron-dense cortical hyaloplasm and its subsequent hypertrophy. Within the cortical hyaloplasm, the fibers of the cytoskeleton may be condensed and course parallel to the plasma membrane which is still intact (Fig. 12).

The third phase (a_3) is characterized by the disruption of the plasma membrane and the formation of overt collagenic fibrils within the electron-dense cortical hyaloplasm (Figs. 12 and 13). The electron-dense hyaloplasm blends into the intercellular matrix locally and the collagenic fibrils are observed forming within it. The fibers of the cytoskeleton are in close apposition to and are ordered parallel with the long axis of the collagenic fibrils (Fig. 13) but are discernible as separate entities from the collagenic fibrils.

Subsequently, in the fourth phase (a_4), the plasma membrane is reformed behind the area of cortical condensation leaving the dense hyaloplasm, cytoskeletal fibers, and the overt collagenic fibrils in an intercellular position (Figs. 12 and 13). The reformation of the plasma membrane occurs at the junction of the endoplasmic and cortical zone.

Contributions of collagenic fibrils to the intercellular areas in the previous manner is indicative of an apocrine-like secretory process. The condensation of the hyaloplasm and cytoskeletal fibers establishes a region of organizing collagenic fibrils. With the disruption of the plasma membrane, the region of organizing collagenic fibrils blends with homologous regions of adjacent cells in such a manner that a common domain is established in which the individual contributions of each cell is not discernible (Fig. 10), but does establish the collagen fiber discernible at the light microscopic level. The deposition of collagenic fibrils and the concomitant loss of cytoplasm increases the distance between the adjacent cells.

Collectively, the newly formed collagenic fibrils in the region around the periphery of the cell where they are

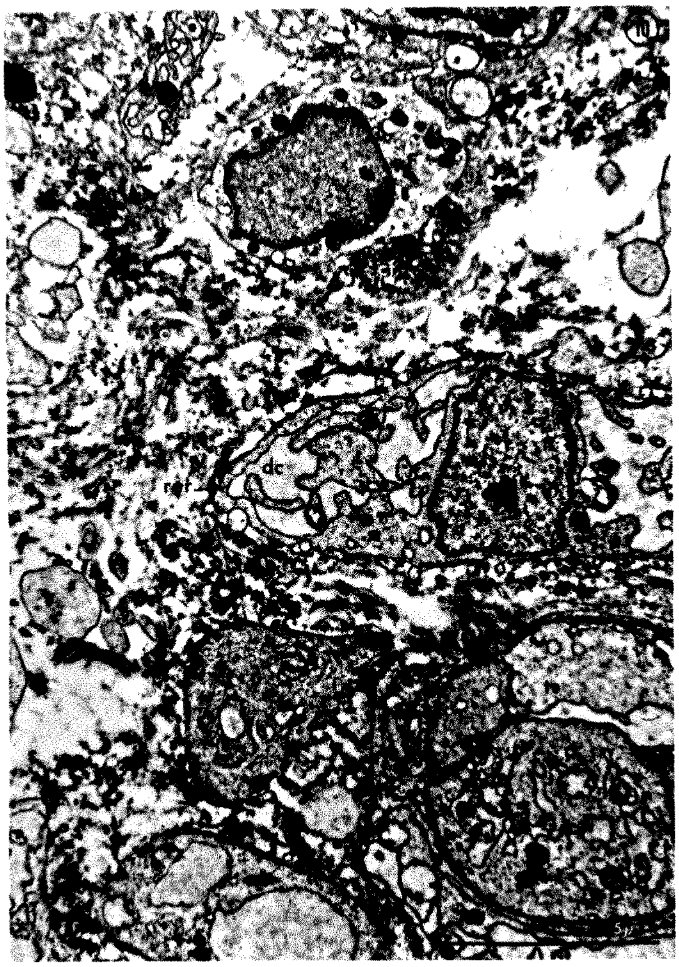


FIG. 10. The cellular peripheral region of the tissue complexes exhibit apocrine-like secretory deposition of collagenic fibrils (cf) into common domains (cr). Some of the fibroblasts possess a rough endoplasmic reticulum (rer) delimiting large dilated cisternae (dc). A cell-lined tissue fluid space (ts) is located in the lower right corner of the micrograph. The tissue complex is 8-weeks-old. (Stained with aqueous uranyl acetate and lead citrate, ×11,842).

organizing, corresponds to the argyrophilic fibers observed at the light microscopic level (compare Fig. 9 to Fig. 12).

The fibroblasts and cell processes located in fibrous zones follow a different recognizable secretory cycle. The fibroblasts undergo an orderly pattern of regression or cytodestruction which is interpreted to be a holocrine-like secretory process. The descriptive phase designations (h_1 through h_3) have been previously used by Richter and Schilling.[58]

In the first (h_1) of holocrine-like deterioration (Fig. 15) an electron-dense cortical hyaloplasmic zone lies adjacent to the plasma membrane. This zone is greatly hypertrophied and may extend totally around the periphery of the cell rather than exist as the localized condensations described in the apocrine-like phases. With the hypertrophy there is a concomitant diminution of the endoplasm. The fibrils of the cytoskeleton described in the apocrine-like phases may be masked due to the density of the hyaloplasm (Fig. 14).

Organelle changes accompanying the h_1 phase indicate a deterioration. The outer nuclear membrane is only partially discernible and the chromatin material is condensed around the nuclear membrane. While a wide spectrum of variation has been noted, the mitochondria are generally reduced in number, enlarged, and contain a granular matrix. The endoplasmic reticulum is reduced in amount and occurs as ill-defined vesicles or fragments of membranes. The ribosomes are either attached to the endoplasmic reticulum or are freely dispersed.

With the disintegration of the plasma membrane, the second phase (h_2) commences (Figs. 15 and 16). Collagenic fibrils form in the cortical condensation in the same manner as described in the apocrine-like secretory process, except the plasma membrane is not re-estab-

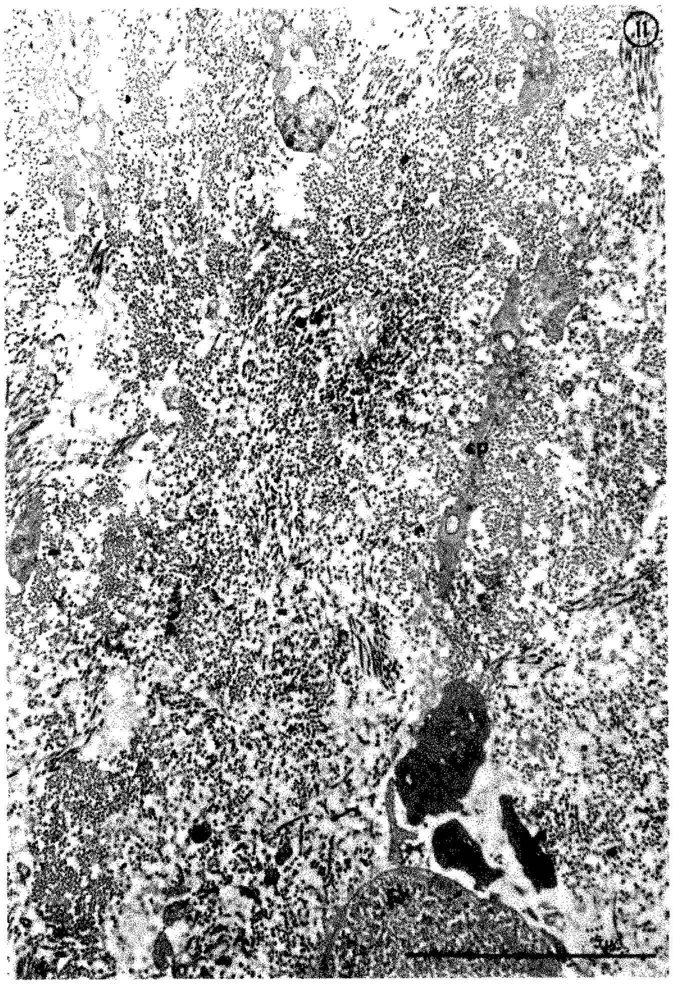


FIG. 11. A fibrous zone of a 16-week-old tissue complex demonstrates a predominantly fibrous character. The electron-dense cytoplasmic processes (cp) and the fibroblast undergoing cytodestruction (cy) are common to this zone. The vast amount of collagenic fibrils taken as a whole comprise the osmiophobic zones of Fig. 1. (Stained with 1% phosphotungstic acid, ×13,176.)

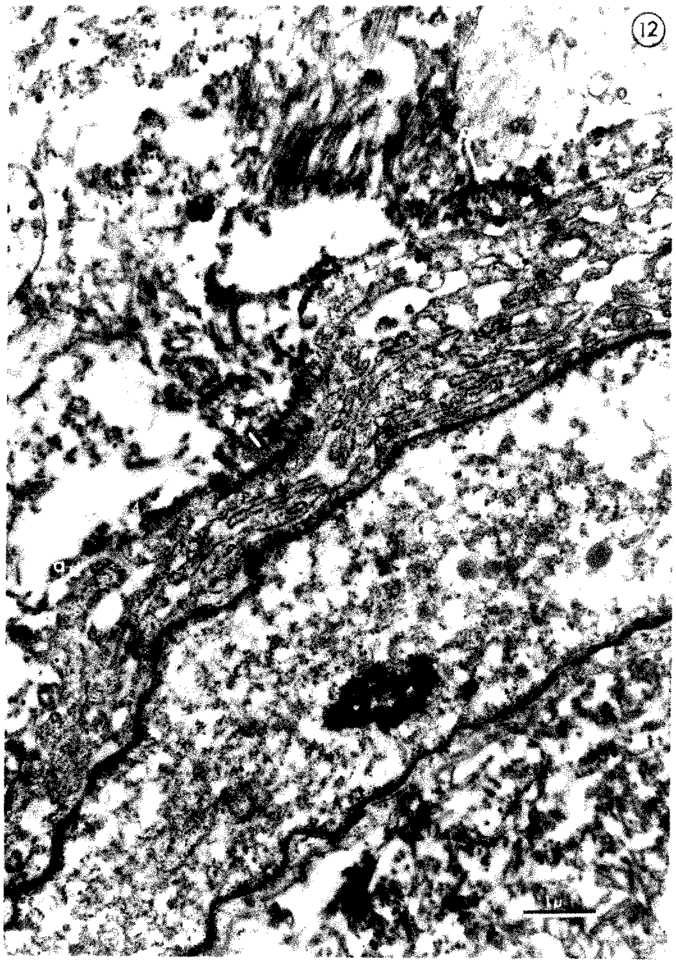


FIG. 12. A fibroblast of the cellular zone of an 8-week-old tissue complex demonstrates the various cell surface changes related to the apocrine-like cyclic phases of fibrillogenesis (a_1 through a_4). The undifferentiated collagenic fibrils in the established regions of organizing fibrils as a whole correspond to the argyrophilic fibers (ar) seen at the light microscopic level. (Stained with a 1% aqueous uranyl acetate and lead citrate, ×19,353).

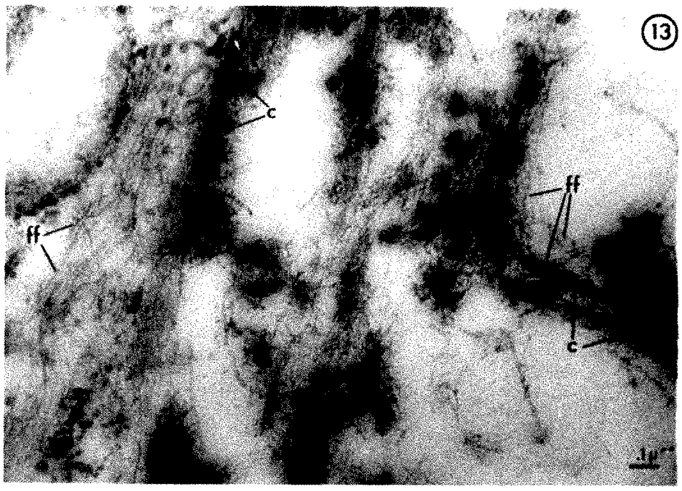
lished. The cell surface is now represented by an electron-dense hyaloplasm containing organizing collagenic fibrils and the associated cytoskeletal fibrils (Figs. 14, 15, and 16). The electron-dense hyaloplasm is greatly hypertrophied and may extend from the arbitrary cell surface to juxtanuclear positions. The nucleus is either of the condensed chromatin type (Fig. 16) or slightly pycnotic.

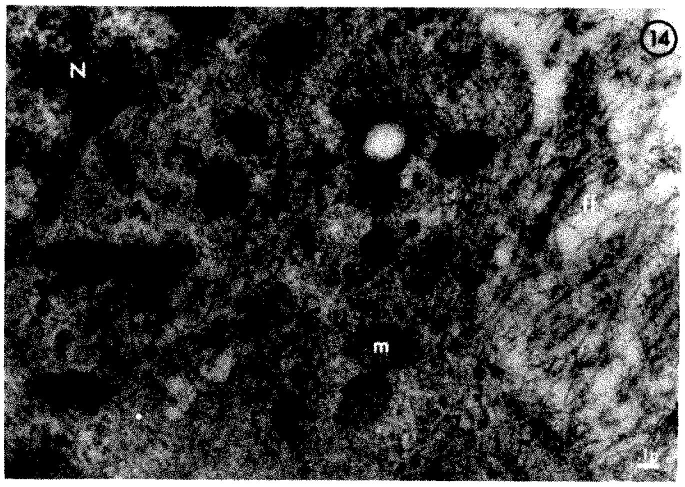
Due to the continued elaboration of collagenic material and regression of the cytoplasmic matrix, the fibroblasts occupying positions at the junction between adjacent cellular and fibrous zones are further removed from adjacent cells. These cells are now deeper in a fibrous zone which they have created around themselves.

With continued holocrine-like deposition of collagen, the cells enter the terminal phase (h_3) of regression and cytodestruction (Figs. 11 and 17). In the final phase (h_3) of cytodestruction, the nucleus of the fibroblast is reduced in size, and the chromatin material is condensed throughout the nucleus (pycnosis). Progressive cytodestruction continues until the nuclear material fragments (karyorrhexis) leaving only nuclear debris.

The endoplasmic reticulum and Golgi complex have usually deteriorated to the point that no recognizable fragments are observable. The only observable structures in the cytoplasm are highly modified, dense, granular mitochondria and free ribosomes which disappear with continued wasting.

Except for an occasional remnant, the plasma membrane has deteriorated leaving the cytoplasmic perimeter





FIGS. 13, 14. FIG. 13. A fibroblast in the apocrine-like phases of collagenic fibril deposition demonstrates the filamentous fibers (ff) of the cytoplasm. The condensed fibers form a part of the cortical condensation (cc) and with the emergence of overt collagenic fibrils (c), the fibers of the cytoskeleton maintain a close relationship. The fibrils measure from 50 Å to 90 Å in diameter. (Stained with aqueous uranyl acetate and lead citrate, ×89,508). FIG. 14. The cytoskeletal fibers (ff) may be masked due to the density of the cortical hyaloplasm in holocrine-like deterioration. Extracellularly, the fibers are readily discernible. Note the variation in mitochondria (m) and the lack of nuclear membranes delimiting the nucleus (N). (Stained with aqueous uranyl acetate and lead citrate, ×55,890).

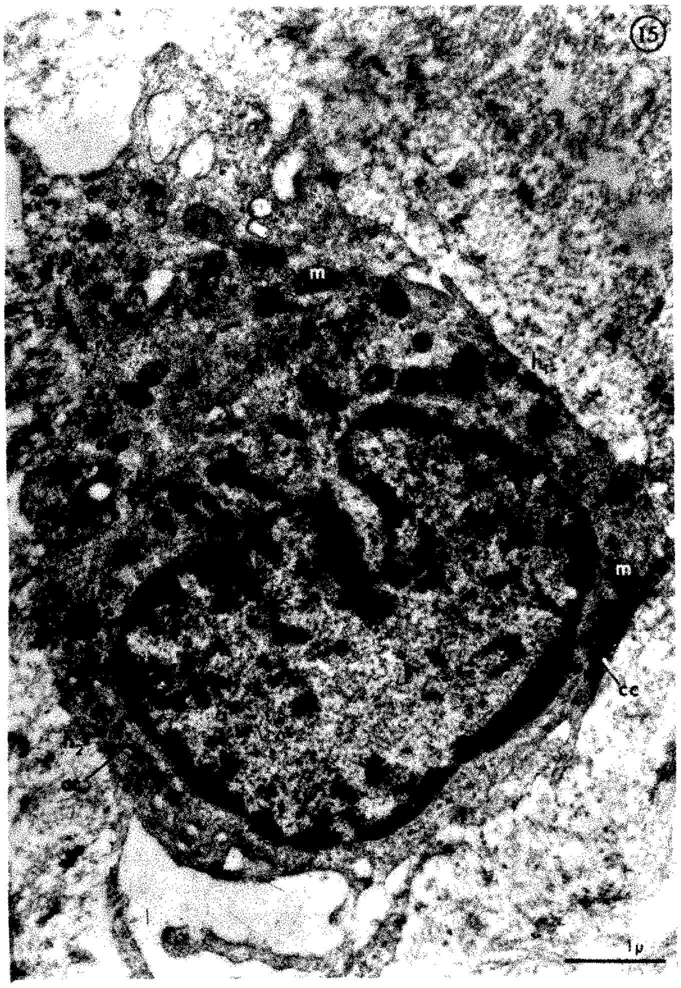


FIG. 15. A fibroblast from the junctional area between a cellular zone and a fibrous zone demonstrates the early phases (h_1 and h_2) of the terminal holocrine-like deterioration. Note the hypertrophied cortical condensation (cc), the enlarged mitochondrion (m) and the dense mitochondrial matrix. (Stained with aqueous uranyl acetate and lead citrate, ×26,281).

marked by a greatly hypertrophied cortical condensation consisting of the electron-dense cortical hyaloplasm, condensed fibrils of the cytoskeleton, and organizing collagenic fibrils. The cytoplasm is now represented by a small amount of perinuclear electron-dense hyaloplasm and insular-like cytoplasmic extensions among the collagenic fibrils (Figs. 18 and 19) which are gradational with the interfibrillar matrix. Collagenic fibrils are observed to form at both the surface of the intracellular hyaloplasm and in the interfibrillar matrix (Fig. 17) which was derived from the cortical hyaloplasm.

The amount of cytoplasm utilized in apocrine-like deposition is minor compared to that utilized in holocrine-like deterioration where fibroblasts contribute almost all of their cytoplasmic mass to the formation of collagenic fibrils and the interfibrillar matrix (compare Figs. 10 and 12 to Figs. 16 and 17). The individual regions of organizing collagenic fibrils in holocrine-like deterioration blend to form a common domain of organizing collagenic fibrils. With differentiation of the fibrils, the common domain is represented by the collagenic fiber discernible at the light microscopic level (compare Figs. 11 and 17 to Fig. 5).

Within the hyaloplasm of cell processes and cells associated with the holocrine-like secretory phases, electron-dense structures occur (Figs. 18 and 19). In terms of density and size, two types of structures can be distinguished; namely, large, very electron-dense, spherical bodies occurring in a random distribution, and smaller, less electron-dense spherical bodies which usually appear in ordered rows. Neither of the two are associated with observable membranous structures. High resolution micrographs (Figs. 20–22) indicate that the smaller structures may be aggregated to form the large structures. The size range of the small structures is from 129.2 Å to

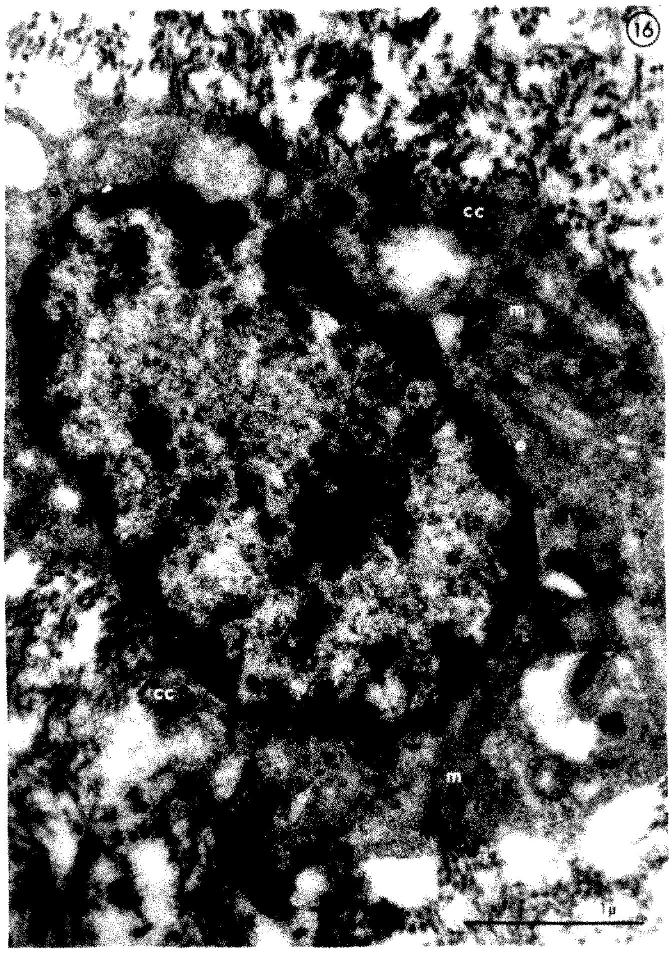


FIG. 16. A fibroblast with a dense clumped chromatin nucleus demonstrates the h_2 phase of holocrine-like deterioration. The cell surface is represented by the cortical condensation (cc) and organizing collagenic fibrils. Note: highly modified mitochondria (m), greatly hypertrophied cortical condensation, small areas of endoplasm (e) containing fragmented endoplasmic reticulum, faintly visible nuclear membrane remnants. (Stained with uranyl acetate and lead citrate, × 48,679).

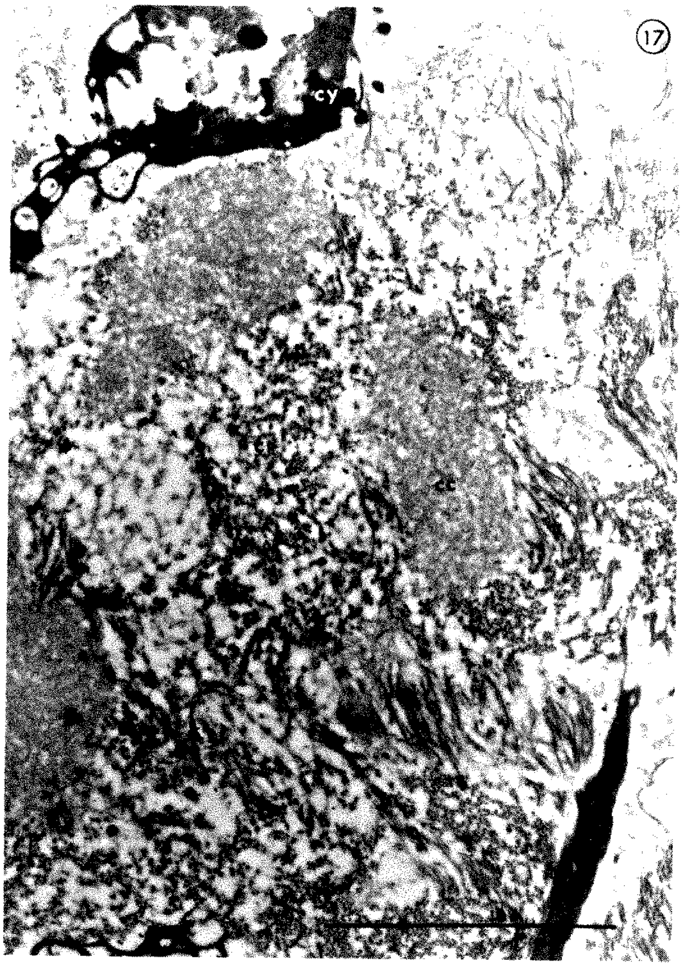


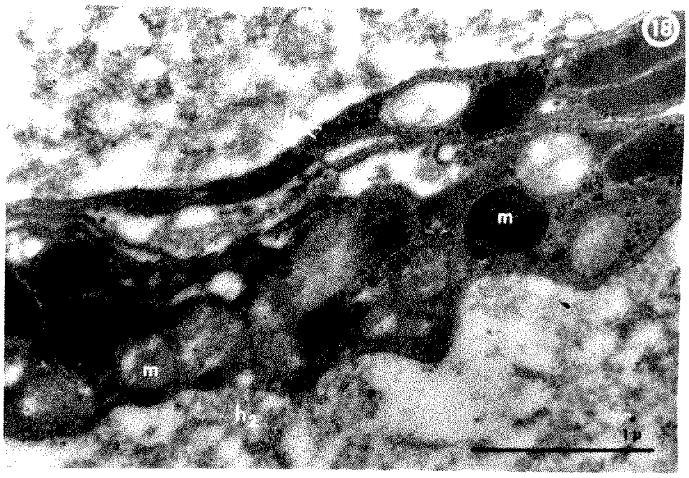
FIG. 17. A fibrous zone of a 12-week-old tissue complex demonstrates the terminal or h_3 phase of holocrine-like deterioration. The fragmented cell demonstrated is in the terminal phase of cytodestruction (cy). Cytoplasmic extensions consisting of non-membrane bounded electron-dense cortical condensation (cc) exist among the already formed collagen fibrils (c) and represent regions of organizing collagenic fibrils contributing to a common domain (cr). (Stained with aqueous uranyl acetate and lead citrate, ×7,764).

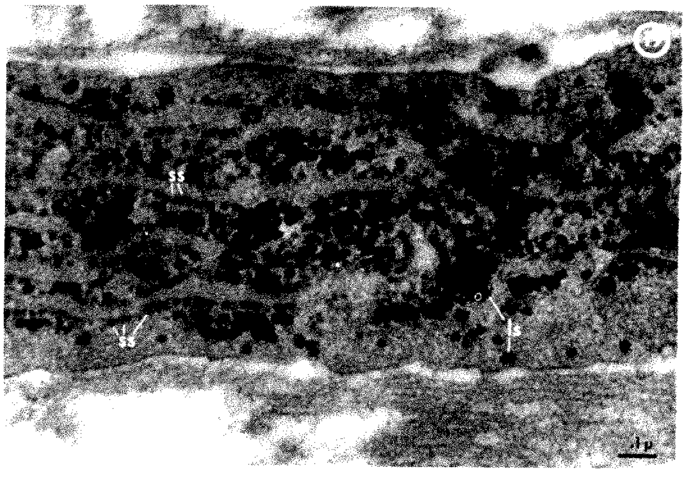
252.5 Å with a mean value of 163.0 Å. The large dense structures are quite variable in size and have measured up to 402.4 Å.

Within the structure of the dense bodies, corpuscular units were observed (Fig. 20). The corpuscular units were in turn comprised of an internal cable or rope-like structure in a coiled configuration with a mean diameter value of 24.9 Å. Simple corpuscular units possessing only one coil (2 cable diameters) around a central axis measure from 55.0 Å to 69.7 Å with a mean value of 64.3 Å. More complex corpuscular units consisting of more than one cable coil measure from 68.6 Å to 129.2 Å with a mean value of 109.4 Å.

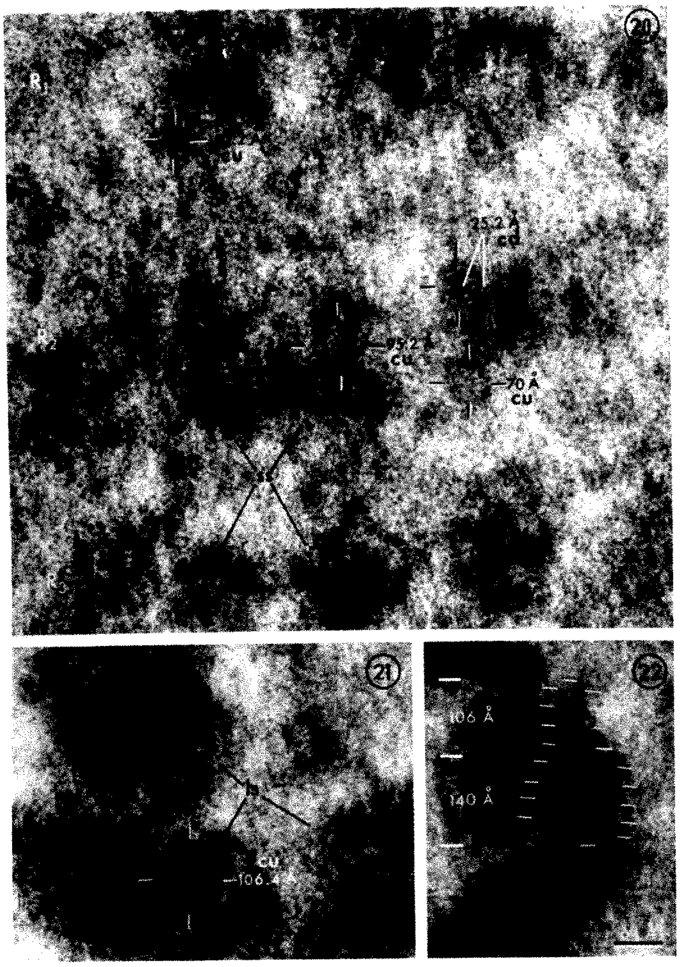
A section through the long axis of one corpuscular unit (Fig. 32) indicates the structure to be pear-shaped (piriform) (Fig. 22). The narrow segment of the pear-shaped unit measures 106 A in the long axis. Its cross-sectional diameter corresponds to the small measurable corpuscular units. The bulbous portion of the pear measures approximately 140 A in the long axis and corresponds in cross-section to the larger corpuscular units. Due to superimposition and various planes of cut, the pear-shaped units are rarely discernible in sections through the long axis.

The collagenic fibrils forming within the hyaloplasm (inter- or intracellular) appear to be undifferentiated. The periodicity measurement is smaller than that of the differentiated fibrils. The average periodicity measurement of the undifferentiated collagenic fibrils is 490.1 A





FIGS. 18, 19. FIG. 18. A cell process extending into a fibrous zone demonstrates changes related to the holocrine-like deterioration phases. Note: mitochondrion (m), dense granule-like structures appearing in the cytoplasm (ls), holocrine-like phases (h_1 and h_2). (Stained with aqueous uranyl acetate and lead citrate, ×48,438). FIG. 19. A cell process demonstrates two types of small, spherical, electron-dense structures. The larger, exceptionally dense structure (ls) has no apparent organization in the cytoplasm. The smaller structure (ss) appears in ordered rows or free in the cytoplasm. Neither structure has apparent membranes associated with them. (Stained with aqueous uranyl acetate and lead citrate, ×99,403).



FIGS. 20-22. FIG. 20. Three ordered rows (R_1, R_2, R_3) of the small electron-dense structures (ss) described in Figure 19 are found to be comprised of circular or corpuscular units (cu) of varying size. Internally the corpuscular unit is comprised of a rope or cable-like structure which is coiled around a central axis to form the corpuscular units. The mean cable diameter (cd) is 24.9 A. FIG. 21. The larger electron-dense structures (ls) described in Fig. 19 appear to be aggregates of the small structures of Figure 20, and would therefore be dense aggregates of corpuscular units (cu). FIG. 22. A section through the long axis of a corpuscular unit demonstrates the configuration to be pear-shaped. The limits of the lower bulbous portion of the pear is not readily discernible due to superimposition of adjacent structures; however, the lower portion measures approximately 140 Å. Note: (Figs. 20–22, stained with aqueous uranyl acetate and lead citrate, ×1,780,380).

(Fig. 23). The conventional bands (a, b, c, and e) within the macroperiod are not readily discernible.

Corpuscular units comprised of an internal cable-like structure are present in the undifferentiated collagenic fibril. The morphologic description and mean value measurements are essentially the same as that described for the electron-dense structures of the cortical hyaloplasm of cells in holocrine-like deterioration.

The differentiated collagenic fibrils in the fibrous zones of the human connective tissue complex have a mean periodicity of 553.0 A (Fig. 24) with the conventional a, b, c, d, and e bands within the structure of the macroperiod. Corpuscular units comparable to those observed in the undifferentiated fibril and the intracellular electron-dense spherical bodies were observed in the differentiated collagenic fibril.

On examining the interfibrillar matrix in areas of fully differentiated collagenic fibrils, it was noted that the fibers of the cytoskeleton were generally reduced in number or not observed at all.

Discussion

General Shape and Ordering

The gross configuration of the human fibrocollagenous tissue complex is regulated by the dimensions of the in-

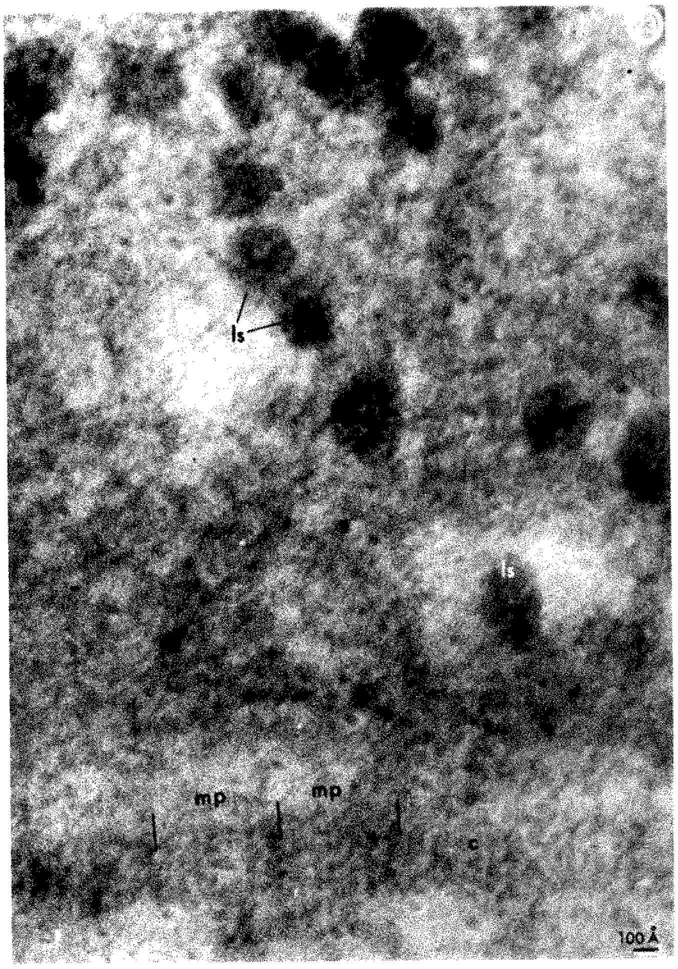


FIG. 23. Within the cytoplasm of a cell process in holocrine-like deterioration a collagenic fibril (c) is organizing in the electron-dense cortical hyaloplasm. The undifferentiated fibril demonstrates a macroperiodicity (mp); however, the a, b, c, d, and e bands within the macroperiod are not discernible as discrete entities. Note the large electron-dense structures (ls). (Stained with aqueous uranyl acetate and lead citrate, ×661,284).

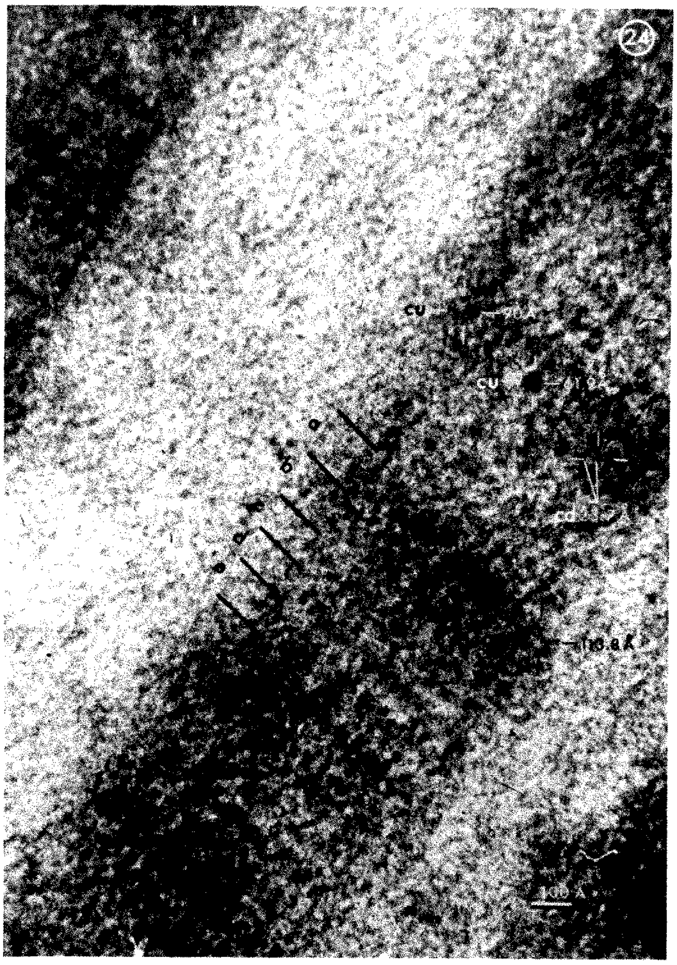


FIG. 24. The differentiated collagenic fibrils of the fibrous zone demonstrates the periodicity associated with collagenic fibrils. Within the macroperiod the conventional a, b, c, d, and e bands are present. Corpuscular units (cu) of varying size are observed within the macroperiod. The corpuscular units have an internal structure which is rope or cable-like. Note: cable diameter (cd), bands of the macroperiod (a, b, c, d, and e). (Stained with 1% aqueous phosphotungstic acid, ×1,053,000).

duction device and as such reflects the size and shape of the sterile dead space which this device imposes upon the superficial fascia. The induction device and its implantation would serve as: 1) an irritant initiating an inflammatory reaction, and 2) a substrate for the peripherally invading connective tissue cells.

The factors perpetrating the lamellated ordering of the alternating fibrous and cellular zones in the tissue complex is at present an incompletely understood process; however, the specific cellular and fibrous features characterizing the lamellations per se correlate directly to the structural and functional changes in the fibroblast during the synthesis of precursory collagenic material, and the organization and deposition *in situ* of overt collagenic fibrils. The lamellated ordering is not peculiar to human subjects. Similar results have been reported using identical devices implanted in the panniculus carnosus of experimental dogs.[54,55,58,67,68] Comparable patterns have been produced using other types of induction devices such as perforated methacrylate tubes and celluloid balls,[17] on the luminal surface of Dacron cylinders used as aortic grafts,[12] and Dacron cylinders suspended in the lumen of the aorta.[44] Other investigators have reported lamellations or have described a lamellated ordering using methods other than mechanical induction devices.[23,31,41,77] The formation of the lamellated pattern appears to be a normal developmental process and is similar to the lamellated pattern of the dura mater or observed in the fibrous periosteum.[31]

Vascularity

The human connective tissue complexes are essentially avascular with a well-developed vascularity outside of the induction device. Other investigators employing different induction devices observed vascularization of connective tissue complexes. Guyton[17] using celluloid balls with 1.0 mm perforations, observed small recurrent vessels located peripherally in the induced tissue. Florey *et al.*,[12] using knitted Dacron cylinders of unknown hole size observed vascularization extending to a point near the lumen of the developing tissue complex. At present, it appears that the factors dealing with vascularization or the lack of it may not be referable to the number or size of perforations in the induction device.

In view of the avascularity of the tissue complex, cell nutrient supplies are probably dependent on properties such as hydrostatic pressures, diffusion gradients, and osmotic pressures. Since the human tissue complex develops as a closed system, diffusion through the interstitial spaces would be a slow process. The cells more peripherally located would, by position, have the advantage in securing nutrient materials needed for specific activity. This would account for the formation and development of the larger fibrous zones located near the periphery.

Fibrous Components

In establishing the fibrous component of the human connective tissue complex, collagenic fibers were the only demonstrable fibers present. The argyrophilic component was interpreted to be immature collagenic fibrils. These small thin collagenic fibrils are reported to be prevalent in developing connective tissue[16] and Dunphy and Udupa[9] have shown that with an increase of demonstrable differentiated collagen, there is a subsequent decrease in argyrophilic fibrils. Further, collagenic argyrophilia has been associated with the small immature collagenic fibrils which are acid or neutral salt soluble.[19,26,81]

The reported observations concerning fibril argyrophilia and electron microscopic observations are consistent with the author's observations.

The negative periodic acid Schiff (PAS) stain reaction is incompletely understood. A positive PAS reaction was reported[58,67,68] in similar studies on dogs. At present biochemical assays performed on the human connective tissue complex indicates the presence of acid and neutral mucopolysaccharides.

Fibroblasts in the Cellular Areas

Fibroblasts in the cellular zones are generally of a normal healthy active appearance. Their structural features conform to those generally described for this cell in various experimental animals[3,4,7,18,28,37,38,46,49,54,55,58,67,68,84] and in the human subject.[64] These fibroblasts are observed to exhibit apocrine-like cyclic phases of fibrillogenesis which has been observed in the fibroblast by other investigators.[6,7,14,50,54,55,58,84] It is the author's observation that in almost every report in the literature utilizing ultrastructural studies on the development of fibrous connective tissue in the healing wound or cells concerned with fibrillogenesis, some phase of the apocrine-like secretory process may be observed.

The fibroblasts located in the fibrous zones are characteristic of cells undergoing cytodestruction or wasting and as observed, contribute the major amount of fibrillar material to the fibrocollagenous tissue complex in a holocrine-like deterioration. This final holocrine-like deterioration in fibrillogenesis has been suggested,[31,49,54,55,58,76] and is observable in the recorded electron micrographs of other investigators.

Fibrillogenesis

Early investigators[18,33,37,73,74] using light microscopes, differential connective tissue stains, and simple biochemical extraction methods described fibrillogenesis as related to specific cell changes. The visualized changes, primarily described by Hansen,[18] have been summarized and reiterated by Richter and Schilling.[58] The gist of this is as follows: It was demonstrated that the source of collagenic fibrils or precursory fibrillar material is the specific connective tissue cell (fibroblast, osteoblast, or chondroblast). The specific collagen producing cell is internally ordered into an endoplasmic mass and an exoplasmic mass which is of variable thickness from area to area within the cell or may be absent within various areas of the same cell. Overt collagenic fibrils form in the cortical exoplasm from precursory collagenic material, with the exoplasm being concurrently converted into intercellular substance, including the ground substance, and the overt collagenic fibrils. This sequence is followed by the continual transformation of endoplasm. At this point, the cell may repeat the apocrine-like sequence or it may enter the holocrine-like deterioration phases. The endoplasm as well as the exoplasm begins to degenerate releasing chondromucoids, albuminoids, or converting directly into that which is destined to become the intercellular substance including the ground substance and overt collagenic fibrils. The degenerating cells are eventually reduced to cytoplasmic remnants between the fibrils and small nuclear masses which gradually waste away. The fibrils widely separated from the decorticated cells undergoing cytodestruction continue to develop and differentiate without the specific conversion of endoplasm into exoplasm.

On examining the above sequence of events, it is noted that fibrillogenesis is a continuous developmental process leading from fibroblastic differentiation to cytodestruction. Further, the apocrine-like phases of fibrillogenesis blend into holocrine-like deterioration without a break in continuity. The extension of this final phase of cytodestruction applied en masse would lead to the formation of a fibrocollagenous structure referable to a cicatrix.

Fibroblast Fine Structure

The active fibroblasts of the cellular zones possess an extensive rough endoplasmic reticulum. The basophilia observed at the light microscopic level and the well-developed rough endoplasmic reticulum are suggested to be related, and indicative of protein synthesis. Specifically, in the fibroblast the rough endoplasmic reticulum or the polysome formations are suggested to be related primarily to the synthesis of collagenic material.[15,28,30,36,39,45,53,78]

The structure of the endoplasmic reticulum is variable within the limits of the same cell and as the density of the hyaloplasm changes, the character of the endoplasmic reticulum also changes. This is readily demonstrated by comparing the nature of the endoplasmic reticulum in the endoplasmic mass to the endoplasmic reticulum or the remnants thereof in an area of hypertrophied cortical hyaloplasm. Various other investigators have observed this variation in structure with the concurrent changes of the hyaloplasm and the endoplasmic reticulum.[6,15,22,30,40,46,58,60–62,64,83]

On the basis of electron microscopic autoradiographic studies,[52,63] it has been suggested that precursory collagenic material is synthesized by the rough endoplasmic reticulum and subsequently attached to the endoplasmic reticulum and Golgi apparatus. Several investigators have reported accumulations of precursory material in the Golgi membranes and endoplasmic reticulum with subsequent fusion of these membranes with the plasma membrane. This effects a merocrine-like secretory function.[15,22,29,52,53] At no time has the authors' work suggested a merocrine-like secretory function and this view is shared by other investigators.[49,58]

The literature and observations indicate the synthesis of precursory collagenic material within the endoplasmic area is associated with the ribosomes and membranes of the endoplasmic reticulum. This precursory material is subsequently accumulated peripherally in the hyaloplasm. The accumulation is either local or throughout the cell surface during the apocrine-like phases of fibrillogenesis or in the endoplasmic mass in the holocrine-like phases. This is followed by the conversion of these areas into the dense cortical hyaloplasm observed and described by other investigators.[6,7,18,21,24,31,49,58,71,72,83]

The variation in mitochondrial fine structure has been noted by other investigators[58] and a similar variation was observed in secretory cells other than fibroblasts.[8] The variation does not seem to relate to the cell secretory cycle uniformly but seems to relate to the individual activity of each mitochondrion independently.

The fine 50 Å to 90Å fibers observed in the general fibroblast cytoplasm, in the hypertrophied cell cortex and associated with collagenic fibrils in various stages of differentiation are visualized by the author as being separate structural entities from the collagenic fibrils to which they are in close contact. The origin, function, and fate of these fibers is unknown. As such, their presence is simply recorded. This approach is shared by other investigators.[6,7,10,24,30,36,46,60,61,64,76,83,85] These filamentous fibers have been suggested by some investigators to be primary or protofibrils upon or around which tropocollagen molecules polymerize to form the overt collagenic fibril.[14,47,49–51,70] While the close relationship of the filamentous fibers does suggest a possible function as an organizer or initiator of polymerization, the filamentous fibers exist and maintain a close relationship to the differentiated fibril as well as the undifferentiated fibril. Further, there is no evidence that these fibrils are incorporated into the collagenic fibril. Other investigators relate the filamentous fibers to a cytoskeleton or cytoplasmic reticulum.[11,22,47,52,54,55,58,76] Due to the filamentous fiber's staining qualities, they are probably made of a structural protein. Further, their ability to exist both intra- and intercellularly and their observed existence from a condensation in the cortex to their continued association with collagenic fibrils through the differentiation of the native fibril alludes to the stability of these fibers. Their ordered condensation in the cortical hyaloplasm would maintain or give support to the structural stability of the membranous components of the cell, particularly the cell surface. Further, with the loss of the plasma membrane during the various phases of fibrillogenesis the condensed cortical cytoskeletal fibers and the electron-dense hyaloplasm would possibly serve as a semipermeable membrane maintaining the cell's integrity.

The previously discussed localized cytoplasmic hypertrophy in the apocrine-like phases and the massive general hypertrophy in the holocrine-like phases of fibrillogenesis are due to the accumulation of precursory collagenic material in the cytoplasm. With the disappearance of the plasma membrane undifferentiated collagenic fibrils begin to organize directly from precursory collagenic material, presumable the basic molecular collagenic unit, tropocollagen contained in the cortical hyaloplasm. The re-establishment of the plasma membrane in the apocrine-like phases or the further regression of the cytoplasm in the holocrine-like phases deposits the respective dense cortical hyaloplasmic masses *in situ* intercellularly.

The undifferentiated fibrils continue to grow and differentiate by incorporation of precursory collagenic material present in the now "intercellular hyaloplasm." The intercellular hyaloplasm would properly be termed the intercellular matrix or, not including the collagenic fibrils and cytoskeletal fibers, the ground substance. The actual amount of hyaloplasm retained as ground substance is unknown but it is suggested the specific connective tissue cells (fibroblast, chondroblast, and osteoblast) do form the ground substance.[13]

Within the "intercellular hyaloplasm" far distant from cells, overt collagenic fibrils continue to form and differentiate indicating that precursory collagenic material is present in the "intercellular matrix." The continued intercellular differentiation correlates with: 1) the loss of argyrophilia previously discussed; 2) the increase in fibril width with time as observed by other investigators;[50,60] and 3) the change in the intermolecular bonding with differentiation as reported by Jackson and Bently.[25]

These sequences or various portions of the sequences involving the apocrine-like or holocrine-like phases of fibrillogenesis have been observed or reported by many investigators and are referenced in the discussion of the apocrine-like and holocrine-like phases. The above sequences demonstrate both the intercellular and intracellular formation of collagen. It is, therefore, suggested that the proponents of either theory would be essentially correct. Further, the ground substance or that portion of the ground substance formed from the hyaloplasm and the collagenic fibrils are deposited *in situ*. These observations are confirmed by other investigators.[28,49,54,55,58]

The broad concept that fibroblast contact is essential to fibrillogenesis is indicated by this investigation. The exact nature of fibroblast contact is not established or defined by previous investigators. It is suggested by the author that the synthesis of precursory collagenic material within the fibroblast, the accumulation of this material, its polymerization, and the deposition *in situ* of overt collagenic fibrils in either the apocrine-like or holocrine-like secretory processes should meet all the requirements of fibroblast contact.

Electron-Dense Hyaloplasmic Structures

The electron-dense hyaloplasmic structures observed in cells and cell processes undergoing holocrine-like phases of fibrillogenesis were arbitrarily typed into two categories based on size and electron density. The larger electron-dense structures are randomly arranged in the cytoplasm and the smaller less electron-dense structures are ordered in rows suggestive of the configuration of ribosomes attached to the endoplasmic reticulum. Neither of the structures are associated with discernible membranes. It should be noted that these electron-dense structures were not observed in fibroblasts in the apocrine-like phases of fibrillogenesis nor in all cells or cell processes undergoing holocrine-like deterioration.

The piriform units comprising the electron-dense structures correlate to a structure of the same approximate size and shape described in native collagen fibrils in dog fibrocollagenous tissue and suggested to be the basic molecular unit comprising the native collagenic fibril, the tropocollagen molecule.[57–59] The piriform unit's configuration is the reflection of an internal asymmetrically coiled cable or rope-like structure which has a mean diameter of 24.9 Å which compares with the 22.9 Å diameter reported by Richter *et al.*[57] and Richter and Schilling.[58,59]

In reviewing the literature, there are no descriptions or electron microscopic visual recordings of the specific electron-dense structures observed by the authors. Further, there has been no direct visual demonstration of the piriform structures within the cell cytoplasm.

The observations of the suggested tropocollagen molecules in the hyaloplasm lends visual evidence to the previously suggested accumulation of precursory collagenic material in the cytoplasm. The discernible presence of these pear-shaped structures in both the organizing fibril and the differentiated fibril is evidence that the collagen fibril is composed of these basic units. Their method of incorporation and organization within the fibril is unknown at this time and serves as a basis for further investigation.

Summary

The growth, development, and cellular activity of specially induced fibrocollagenous tissue complexes in humans has been studied during the time course of fibroplasia utilizing both light and electron microscopic procedures.

The developed fibrocollagenous tissue complexes reflect the essential size and shape of the induction device. Tissue complexes retrieved after 2 to 3 weeks of development consist primarily of fibroblasts. The tissue complexes reclaimed after 4 to 16 weeks of development demonstrate ordered lamellations consisting of zones composed predominantly of fibroblasts and zones consisting primarily of collagenous fibers. The development of the lamellations is referable to the specific fibrillogenic activities by the constituent fibroblasts.

The sequence of the morphological aspects of fibrillogenesis occurring in the cellular zones is indicative of an initial apocrine-like role by the fibroblast. Continued fibrillogenesis by the fibroblast eventually terminates in a holocrine-like role resulting in cytodestruction and concurrent formation of a predominantly collagenic fibrous zone.

Fibroblasts active in fibrillogenesis exhibit sequential changes in the cytoplasm involving hypertrophy of the hyaloplasm either locally in the apocrine-like role or generally in the holocrine-like role. The hypertrophy is presumably due to the accumulation of precursory collagenic material within the hyaloplasm. Subsequently, the plasma membrane disappears either locally or generally and overt collagenic fibrils form in the hypertrophied hyaloplasm.

The plasma membrane reforms internal to the hypertrophied hyaloplasmic mass in the apocrine-like function depositing the organizing collagenic fibrils and the hyaloplasmic mass extracellularly. The plasma membrane is not reformed in the holocrine-like function. The deposition of hyaloplasm and organizing fibrils is continuous as the cell terminates itself by cytodestruction. The organizing collagenic fibrils continue to grow and differentiate intercellularly presumably by the incorporation of precursory collagenic material in the interfibrillar hyaloplasm.

The organizing collagenic fibrils are related to argyrophilic fibrils supporting the concept that certain reticular fibers are collagenic in nature. The morphological aspects of fibrillogenesis supports the concept that the fibroblast functions in the synthesis and organization of collagenic fibrils. Further, both the intra- and intercellular concepts of fibrillogenesis is suggested.

The structural relationship of the hypertrophic fibroblast cytoplasm and the emerging collagen fibrils supports and extends the broad concept that fibroblast contact is essential to fibrillogenesis.

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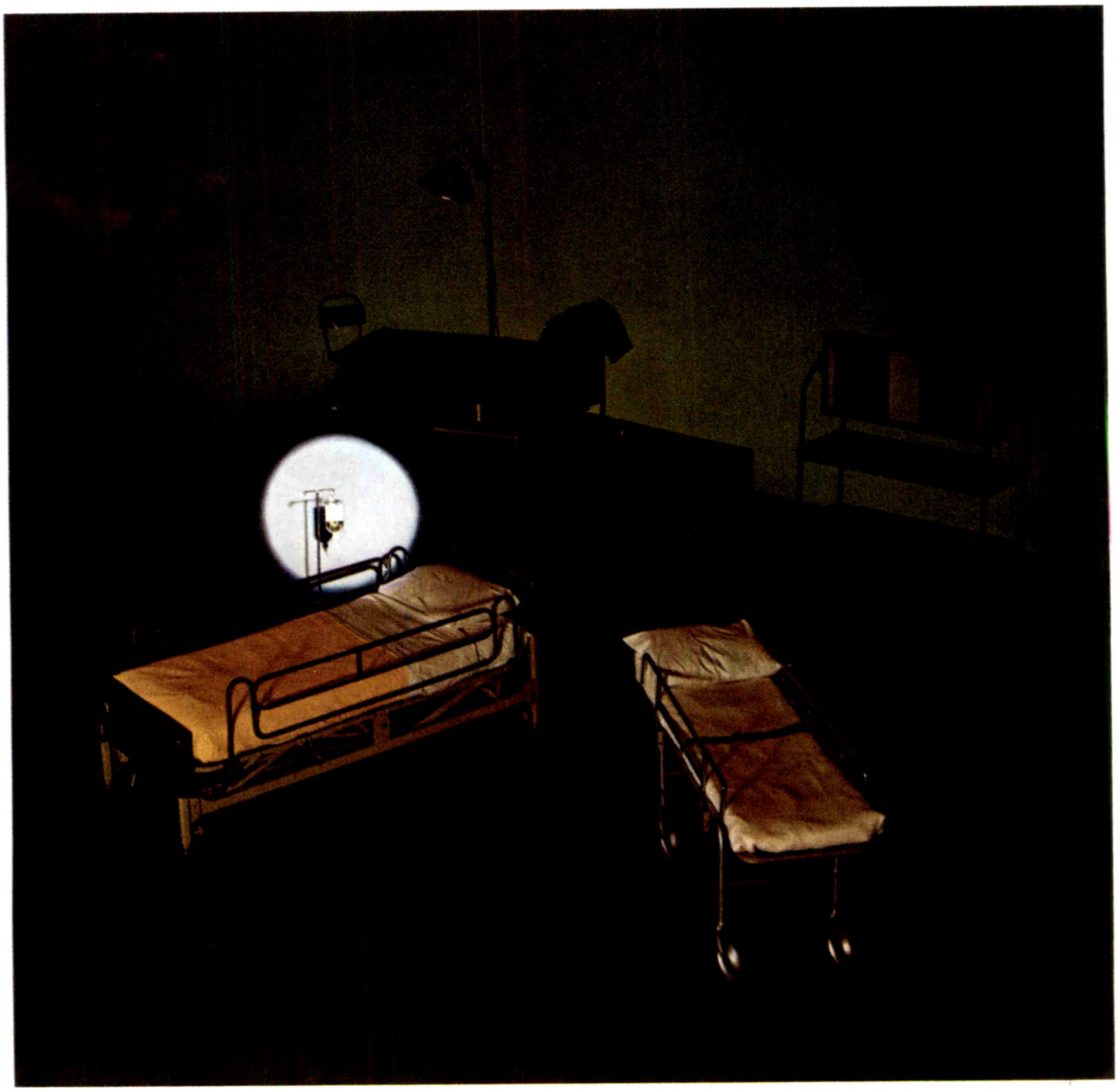

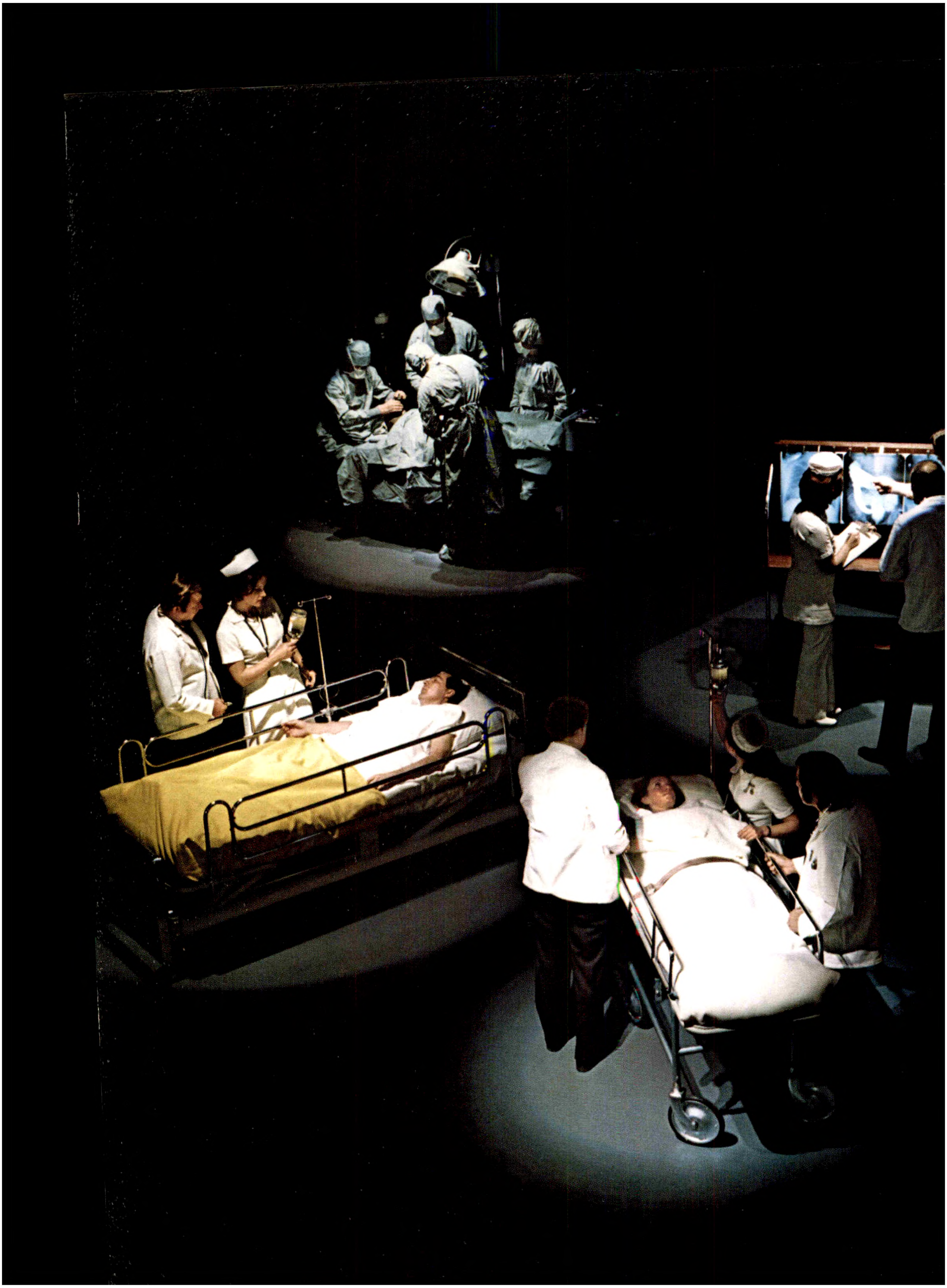

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Flexible Dosage: adjustable to fit severity of infection and renal status of patient:

The usual adult dose of Cefadyl is 0.5 Gm. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. Doses up to 12 Gm. daily may be used in very serious or life-threatening infections.

No nephrotoxicity reported during extensive clinical trials

In fact, when Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported. However, renal status of patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate. Rises in BUN have been observed; their frequency increases in patients over 50 years old.

Low incidence of venous irritation on I.V. administration... well tolerated locally

In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low. *Controlled studies* in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly.

Cephalosporins are reported to produce maculopapular rash, urticaria, reactions resembling serum-sickness and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

In penicillin-allergic patients, cephalosporins should be used with great caution. There is clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins, and there are instances of patients who have had reactions to both drugs (including fatal anaphylaxis after parenteral use).

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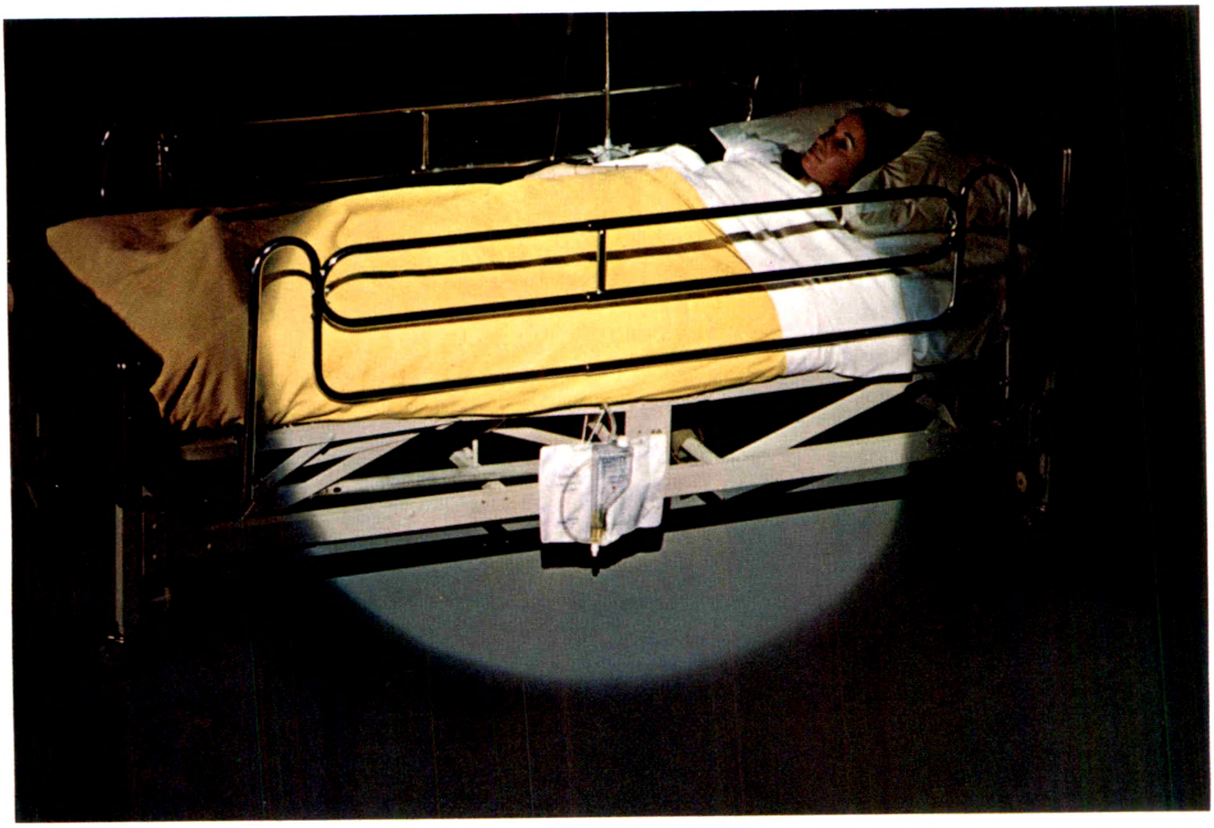

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A new parenteral cephalosporin from Bristol Laboratories

CEFADYL® (sterile cephapirin sodium)
7628 DIRO-04 March, 1974

Description. Cefadyl (sterile cephapirin sodium) is a cephalosporin antibiotic intended for intramuscular and intravenous administration only. It is supplied as the sodium salt of 7-[α-(4-pyridylthio)-acetamido]-cephalosporanic acid. Each 500 mg. contains 1.07 milliequivalents of sodium.

Actions. *Human Pharmacology*—Following intramuscular administration of single 500 mg. and 1 Gm. doses to normal volunteers, average peak serum levels of 9.0 and 16.4 mcg./ml. respectively, were attained at 30 minutes, declining to 0.7 and 1.0 mcg./ml. respectively, at 4 hours and 0.2 and 0.3 mcg./ml. respectively, at 6 hours.

Cefadyl and its metabolites were excreted primarily by the kidneys. Antibiotic activity in the urine was equivalent to 35% of a 500 mg. dose 6 hours after I.M. injection and to 65% of a 500 mg. dose 12 hours after injection. Following an I.M. dose of 500 mg., peak urine levels averaged 900 mcg./ml. within the first 6 hours.

Following rapid intravenous administration of single 0.5 Gm., 1 Gm., and 2 Gm. doses, peak serum levels of 35, 67 and 129 mcg./ml. respectively, were attained at 5 minutes, declining to 6.7, 14.0 and 31.7 mcg./ml. respectively, at 30 minutes and 0.27, 0.61 and 1.11 mcg./ml. respectively, at 3 hours.

Seventy percent of the administered dose was recovered in the urine within 6 hours. Repetitive intravenous administration of 1 Gm. doses over 6-hour periods produced serum levels between 4.5 and 5.5 mcg./ml.

44 to 50% of Cefadyl is bound to human serum. The average serum half-life of Cefadyl in patients with normal renal function is approximately 36 minutes.

The major metabolite of cephapirin is desacetyl cephapirin which has been shown to contribute to antibacterial activity.

Controlled studies in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly. In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low.

Microbiology—*In vitro* tests demonstrate that the action of cephalosporins results from inhibition of cell-wall synthesis. Cefadyl is active against the following organisms *in vitro*:

Beta-hemolytic streptococci and other streptococci. (Many strains of enterococci, e.g., *S. faecalis*, are relatively resistant.) Staphylococci, including coagulase-positive, coagulase-negative, penicillinase and non-penicillinase producing strains. *Diplococcus pneumoniae, Haemophilus influenzae, Proteus mirabilis, Escherichia coli,* Klebsiella species.

Most strains of enterobacter and indole-positive Proteus *(P. vulgaris, P. morganii, P. rettgeri)* are resistant to Cefadyl. Methicillin-resistant staphylococci, Serratia, Pseudomonas, Mima and Herellea species are almost uniformly resistant to Cefadyl.

Disc Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to cephalosporin class antibiotics. Interpretations correlate diameters of the disc test with MIC values for Cefadyl. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Indications. Cefadyl is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Group A beta-hemolytic streptococci: Skin and soft tissue infections. Respiratory infections.

(Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefadyl is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cefadyl in the subsequent prevention of rheumatic fever are not available at present.)

Staphylococcus aureus (penicillinase producing and non-penicillinase producing): Skin and soft tissue infections. Urinary tract infections.

Diplococcus pneumoniae: Respiratory tract infections.

Haemophilus influenzae: Respiratory tract infections.

Escherichia coli: Urinary tract infections, skin and soft tissue infections and bacteremia.

Klebsiella species: Urinary tract and respiratory tract infections.

Proteus mirabilis: Urinary tract infections.

Note: Appropriate bacteriological studies should be performed to identify the causative organisms and determine its susceptibility. Therapy may be started while awaiting results of these studies.

Contraindications. Cefadyl (sterile cephapirin sodium) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings. IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exceptions should be made with regard to Cefadyl.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions. The renal status of the patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate (see *Dosage, Adults*). When Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported.

Prolonged use of Cefadyl may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Adverse Reactions. *Hypersensitivity*—Cephalosporins were reported to produce the following reactions: maculopapular rash, urticaria, reactions resembling serum-sickness, and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—During large scale clinical trials, rare instances of neutropenia, leukopenia, anemia were reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs test during therapy with other cephalosporins.

Liver—Elevations in SGPT or SGOT, alkaline phosphatase, and bilirubin have been reported.

Kidney—Rises in BUN have been observed; their frequency increases in patients over 50 years old.

Dosage. *Adults*—The usual dose is 500 mg. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. The lower dose of 500 mg. is adequate for certain infections, such as skin and soft tissue and most urinary tract infections. However, the higher dose is recommended for more serious infections.

Very serious or life-threatening infections may require doses up to 12 Grams daily. The intravenous route is preferable when high doses are indicated.

Depending upon the causative organism and the severity of infection, patients with reduced renal function (moderately severe oliguria or serum creatinine above 5.0 mg./100 ml.) may be treated adequately with a lower dose, 7.5 to 15 mg./Kg. of cephapirin every 12 hours. Patients with severely reduced renal function and who are to be dialyzed should receive the same dose just prior to dialysis and every 12 hours thereafter.

Children—The dosage is in accordance with age, weight and severity of infection. The recommended total daily dose is 40 to 80 mg./Kg. (20 to 40 mg./lb.) administered in four equally divided doses.

The drug has not been extensively studied in infants; therefore, in the treatment of children under the age of three months the relative benefit/risk should be considered.

Therapy in beta-hemolytic streptococcal infections should continue for at least 10 days.

Where indicated, surgical procedures should be performed in conjunction with antibiotic therapy.

Administration. Cefadyl may be administered by the intramuscular or the intravenous routes.

Intramuscular Injection—The 1 Gm. vial should be reconstituted with 2 ml. of Sterile Water for Injection, U.S.P. Each 1.2 ml. contains 500 mg. of cephapirin. All injections should be deep in the muscle mass.

Intravenous Injection—The intravenous route may be preferable for patients with bacteremia, septicemia, or other severe or life-threatening infections who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending. If patient has impaired renal function, a reduced dose may be indicated (see *Dosage, Adults*). In conditions such as septicemia, 6 to 8 Gm. per day may be given intravenously for several days at the beginning of therapy; then, depending on the clinical response and laboratory findings, the dosage may gradually be reduced.

When the infection has been refractory to previous forms of treatment and multiple sites have been involved, daily doses up to 12 Gm. have been used.

Intermittent Intravenous Injection—The contents of the 1 Gm. vial should be diluted with 10 ml. or more of diluent and administered slowly over a 3 to 5 minute period or may be given with intravenous infusions.

Intermittent Intravenous Infusion with Y-Tube—Intermittent intravenous infusion with a Y-type administration set can also be accomplished while bulk intravenous solutions are being infused. However, during infusion of the solution containing Cefadyl (sterile cephapirin sodium), it is desirable to discontinue the other solution. When this technique is employed, careful attention should be paid to the volume of the solution containing Cefadyl so that the calculated dose will be infused.

Continuous Intravenous Infusion—After reconstitution, Cefadyl may be added to the solutions listed below under *Stability*. The choice of solution and volume should be dictated by the fluid and electrolyte management of the patient.

Stability. *Storage Stability:* Cefadyl is stable in the dry state for 18 months at room temperature. After reconstitution, it is stable for 12 hours at room temperature and 10 days under refrigeration when reconstituted with Sterile Water for Injection, U.S.P. The pH of the resultant solution ranges from 6.5 to 8.5. During these storage conditions, no precipitation occurs. A change in solution color during this storage time does not affect the potency.

Compatibility with the Infusion Solutions: Cefadyl is stable and compatible for 24 hours at room temperature at concentrations between 2 mg./ml. and 30 mg./ml. in the following solutions:

Sodium Chloride Injection, U.S.P., 5% W/V Dextrose in Water, U.S.P., Sodium Lactate Injection, U.S.P., 5% Dextrose in Normal Saline, U.S.P., 10% Invert Sugar in Normal Saline, 10% Invert Sugar in Water, 5% Dextrose + 0.2% Sodium Chloride Injection, U.S.P., Lactated Ringer's with 5% Dextrose, 5% Dextrose + 0.45% Sodium Chloride Injection, U.S.P., Ringer's Injection, U.S.P., Lactated Ringer's Injection, U.S.P., 10% Dextrose Injection, U.S.P.

Supply. Cefadyl (sterile cephapirin sodium) for I.M. or I.V. injection. Cephapirin sodium equivalent to 1 Gm. cephapirin. **NDC** 0015-7628-1-Gm. vial.

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*Bauer, A.W., Kirby, W.M.M., Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol., 45:493, 1966. Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972.

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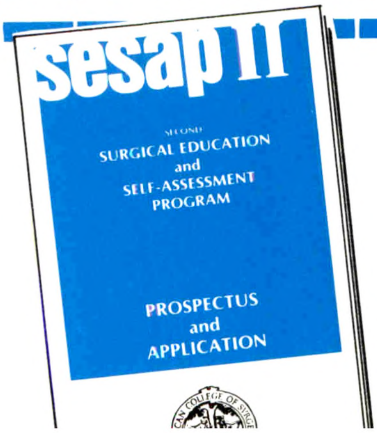
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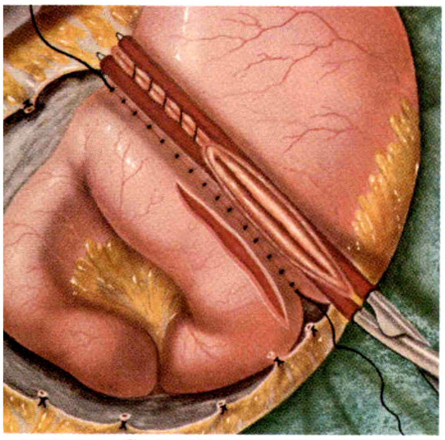
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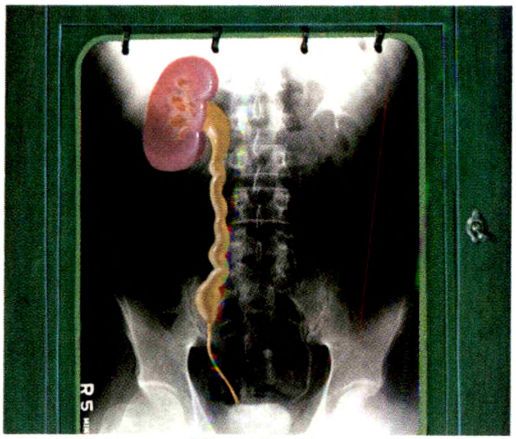

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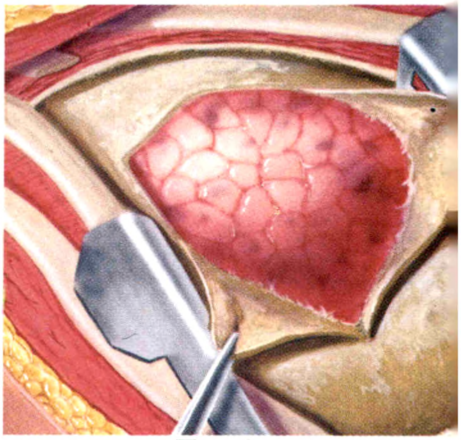
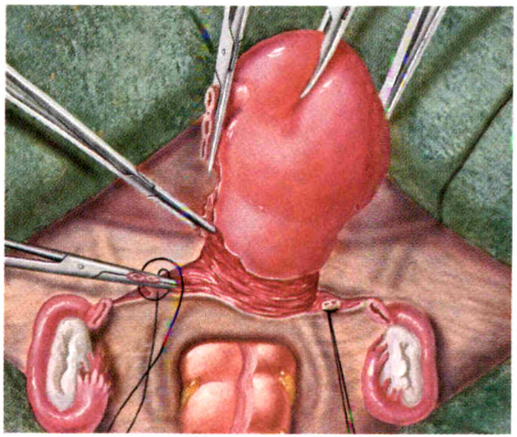
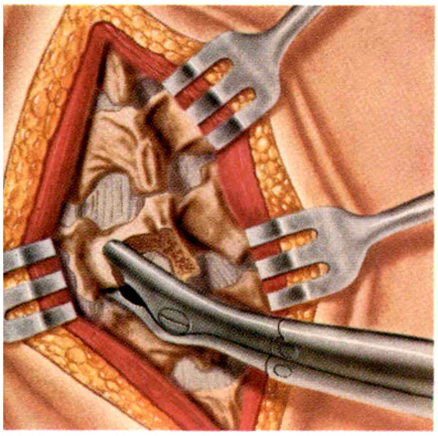

Thoracic surgery

Traumatic pain


Hysterectomy

Endoscopy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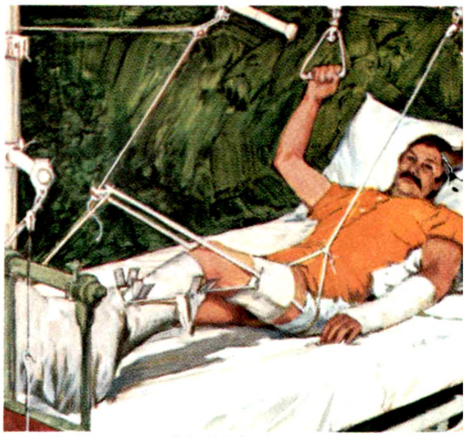
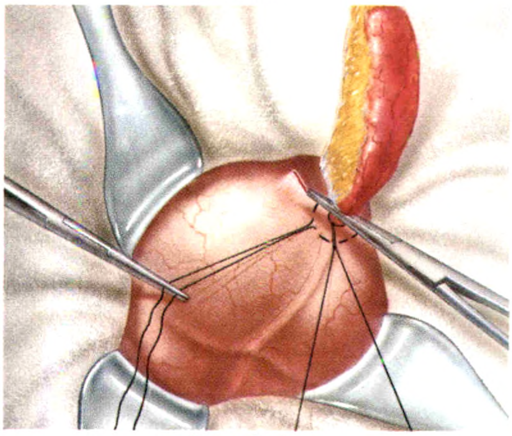
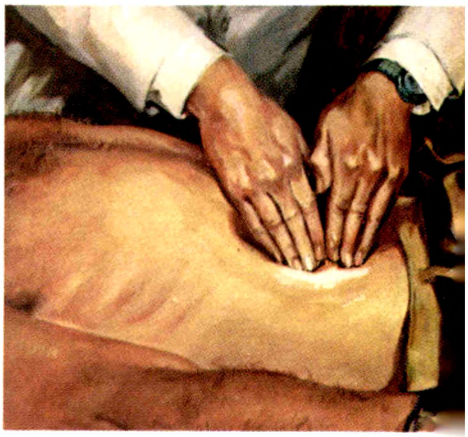
Burns


Multiple fractures

Acute bursitis


Appendectomy


Intestinal colic

Since clinical experience in children under 12 years of age is limited, the use of Talwin (brand of pentazocine, as lactate) in this age group is not recommended. Since sedation, dizziness, and occasional euphoria

the unextreme injectable for serious pain

Talwin doesn't go to extremes.

Yet, Talwin relieves serious pain (moderate to severe pain) in the great majority of everyday hospital situations.

For most serious pain – Talwin has in fact been shown comparable to narcotics such as morphine and meperidine, in analgesic efficacy... with less likelihood of some of the extreme adverse effects produced by the opiates in general.

With Talwin there is a low incidence of respiratory depression, hypotension, urinary retention, and constipation.

In moderate to severe pain

Injectable Talwin®
brand of
pentazocine
(as lactate)

extremely effective for most patients

30 mg. 45 mg. 60 mg.

See important product information concerning warnings, adverse reactions, patient selection, prescribing and precautionary recommendations on last page of this advertisement.

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), **45 mg.** (1½ ml.), **and 60 mg.** (2 ml.)
Vials: (10 ml.) **30 mg./ml.**
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; *dermatologic:* soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Uni-Amp*T.M.*—Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.)* in boxes of 25.

Ampuls of 1½ ml. (45 mg.) in boxes of 10, 25, and 100.

Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for Injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

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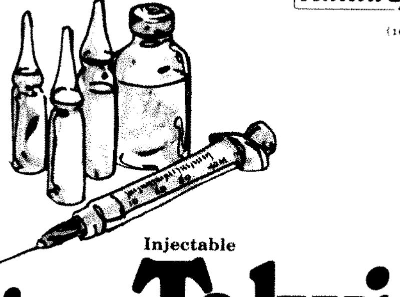

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The Nature and Significance of Hyperamylasemia Following Operation

RICHARD MORRISSEY, M.D., J. EDWARD BERK, M.D.,
LOUIS FRIDHANDLER, Ph.D., DANIEL PELOT, M.D.

Total serum amylase activity was found to be significantly elevated postoperatively in 11 (10%) of 110 patients undergoing various surgical procedures. Isoamylase analysis revealed that the rise was chiefly in the pancreatic-type isoamylase in seven of the 11 patients showing postoperative serum amylase elevations; in the other four patients, the elevation occurred principally in the salivary-type isoamylase. These data demonstrate that postoperative hyperamylasemia occurs surprisingly often and that serum amylase activity may rise even when the surgical procedure is extra-abdominal. Moreover, elevation of serum amylase activity after surgery is not necessarily an indication of pancreatitis and may reflect instead a rise in salivary-type isoamylase.

From the Gastroenterology Division of the Department of Medicine, University of California, Irvine, California

THE DIAGNOSIS of acute pancreatitis complicating the postoperative state[1,11,13,14,19,22] usually is founded on the presence of hyperamylasemia. Since amylase activity may be affected by a variety of factors and conditions, not all directly involving the pancreas, there is an element of uncertainty attaching to the diagnosis of acute postoperative pancreatitis when based on a rise in serum amylase.[19] Moreover, Harada *et al.*[11] have recently presented evidence indicating that the origin of the elevated serum amylase occurring after operations may not always be pancreatic. It would be of decided clinical value, therefore, to know the specific source of the serum amylase which may rise after an operation. This report concerns a study of the isoenzyme pattern of the serum amylase elevation occurring in patients undergoing various operative procedures. Not only was serum amylase activity found to increase often after surgical procedures, but the rise was not always in the pancreatic-type component.

Materials and Methods

A randomly selected group totalling 110 patients undergoing various surgical procedures was studied. Serum was obtained prior to operation and again approximately 3, 24 and 48 hours after operation. Due to circumstances beyond control, including duration of the operation, it was not possible to secure postoperative samples in some of the cases at the precise intervals stated. An additional blood sample was taken 7 days after operation in those patients showing serum amylase elevations during the first 48 hours following operation. Each serum sample was assayed for amylase activity using an automated saccharogenic method.[8] This method expresses amylase activity in terms of mg of glucose generated per 100 ml. The presently adopted upper limit of normal for serum amylase activity by this method, based on a limited analysis of normal subjects, is approximately 100 mg glucose/100 ml.[9]

The serum samples of those patients whose postoperative levels were greater than 50 mg glucose/100 ml above the corresponding preoperative value were further analyzed for isoamylase pattern using methods previously described.[9] These methods separate serum amylase that arises from the pancreas (P-type) from another component (S-type) that originates in the salivary glands and possibly in other tissues as well. Serum amylase was considered to be elevated when the total serum amylase in any postoperative sample exceeded

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TABLE 1. *Summary of Serum Amylase Changes Following Various Operations*

Type of Operation		Serum Amylase Elevations	Isoamylase Mainly Responsible for Elevation	
			Pancreatic Type	Salivary Type
Abdominal	28	4 (14%)	3	1
Non-Abdominal	82	7 (9%)	4	3
TOTAL	110	11 (10%)	7	4

100 mg glucose/ml *and* the activity of either the P-type or S-type components exhibited a rise of at least 100% above the corresponding preoperative value.

Results

Of the 110 patients surveyed, 11 (10%) met the criteria for significant postoperative elevation of serum amylase activity (Tables 1 and 2). Table 2 lists the operations performed and shows the pre- and postoperative levels of the individual isoamylases in those patients showing a postoperative elevation. Representative cases illustrating the changes occurring postoperatively in the major isoamylase components are shown in Fig. 1.

Four (14%) of the 28 patients undergoing abdominal procedures met the criteria for a rise in serum amylase (Tables 1 and 2). In the two patients with the most marked elevations in this group (Cases 6 and 7), the amylase rise was mainly in the P variety. Of the other two patients in this group, the rise was in the P-type in one (Case 3) and the S-type in the other (Case 10).

Eighty-two of the patients had non-abdominal surgical procedures and 7 (9%) showed a postoperative serum amylase rise by the criteria employed (Tables 1 and 2). The elevation was essentially of the S-type isoamylase in 3 (Cases 8, 9, 11) and of the P-type isoamylase in 4 (Cases 1, 2, 4, 5).

When the amylase levels rose significantly in the postoperative period, the peak usually appeared about 24 hours after operation (Fig. 2). Sixty-five of the 110 patients showed an initial drop in amylase activity at three hours after operation. Within 24 hours, the serum amylase either rose above normal, returned to preoperative levels, or maintained the level exhibited at three hours. Isoamylase analysis in two patients showing a diminution in serum amylase in the immediate postoperative period revealed that both the S- and P-components dropped, the more pronounced reduction occurring in the P variety.

Most operations that were followed by serum amylase elevations were done under general anesthesia. However, a cataract removal (Case 1), which was followed by a 320% rise of the P-type, was performed under local anesthesia. Meperidine and hydroxyzine HCL were given to this patient preoperatively.

Four patients exhibited preoperative total serum amylase levels greater than 130 mg glucose/ml (130–180) and thus had values above our presently accepted upper limit of 100 mg glucose/ml. Nine other patients had serum amylase levels above 110 mg glucose/ml both pre- and postoperatively. One of this group with levels of 255 and 225 mg glucose/ml, respectively, was subsequently found to have macroamylasemia using a rapid microcolumn chromatographic method.[10]

Discussion

Reports dealing with acute pancreatitis and hyperamylasemia in the postoperative period have dealt primarily with patients subjected to surgical procedures in the upper abdomen. Thus Perryman and Hoerr[18] reported on 85 patients undergoing upper abdominal surgical procedures. Twenty-seven (32%) had postoperative elevations of serum amylase. Included among

TABLE 2. *Comparative Serum Amylase Levels Before and 24 Hours After Operation in Patients Exhibiting Postoperative Rises*

Case	Surgical Procedure	Serum Amylase Values*					
		Preoperative			24 Hrs. Postoperative		
		P-type	S-type	Total	P-type	S-type	Total
1	Cataract Removal	32	25	57	103	25	128
2	Patellectomy	30	46	76	96	36	132
3	Vagotomy and Pyloroplasty	66	58	124	147	46	193
4	Facial Fracture Repair	34	30	64	81	37	118
5	Spinal Fusion	50	9	59	130	13	143
6	Aortic Aneurysm Repair	22	14	36	924	176	1100
7	Hepatectomy	40	32	72	732	68	800
8	Tendon Repair	26	60	86	30	596	626
9	Arthroplasty	37	74	111	42	180	222
10	Appendectomy	15	19	34	15	170	185
11	Open reduction & Internal Fixation of a Fractured Femur	22	25	47	47	883	930

* Expressed as mg glucose/100 ml.
Postoperative values underlined are those showing rises as defined in text.

the latter were two fatal cases of pancreatitis. However, only a few of the other patients with a postoperative serum amylase rise had clinical findings suggestive of pancreatitis. Mahaffey *et al.*[14] reported that nine (9%) of 100 patients were considered by them to have developed hyperamylasemia following abdominal surgery. Singh *et al.*[19] found that of 95 patients who underwent abdominal operations, 24 had an elevation in serum amylase. These observers also noted that patients with the highest serum amylase levels postoperatively did not develop clinical signs of pancreatitis, whereas patients developing fatal pancreatitis had only moderate serum enzyme elevations. Harada *et al.*[11] studied serum amylase behavior before and after surgical procedures in 114 patients. Of 75 patients undergoing abdominal procedures, 13 developed hyperamylasemia. Another group of 24 patients was separately classified as having procedures done under spinal anesthesia. Although the precise nature of these procedures was not given in detail, appendectomy was noted to have been among them. Five of the 24 patients in this category developed hyperamylasemia. Keighley and co-workers[12] noted postoperative hyperamylasemia in 13 of 107 patients undergoing upper abdominal operations, only three of whom were symptomatic. Bardenheier and associates[1] studied 840 patients who underwent cholecystectomy; 180 also had common bile duct exploration. Thirty-four (4%) of the 840 had clinically evident pancreatitis. In addition, of the 547 patients without clinical signs of pancreatitis in whom amylase determinations were made, 52 had hyperamylasemia (greater than 200 Somogyi units).

Hyperamylasemia and pancreatitis have also been reported postoperatively in patients with extra-abdominal operations.[11,13,19,22] Illustrative is the report of Levine *et al.*[13] which describes 6 cases of necropsy-confirmed pancreatitis following transurethral resection of the prostate. Anesthesia in these cases varied from spinal to general. Singh *et al.*[19] found that 17 of 80 patients undergoing various extra-abdominal procedures developed hyperamylasemia postoperatively. Of the series of 114 patients observed by Harada *et al.*,[11] 15 underwent extra-abdominal procedures. In addition, some of the 24 patients they classified as having minor operations performed under spinal anesthesia probably had non-abdominal procedures. Of the 15 patients in whom the operative procedure clearly did not involve the abdomen, none developed hyperamylasemia. By contrast, five of the 24 patients who were operated on under spinal anesthesia developed hyperamylasemia.

Mahaffey *et al.*[14] found that none of 31 patients who underwent operative procedures not involving the abdomen developed hyperamylasemia by their criteria. White *et al.*[22] reported on 70 cases of postoperative

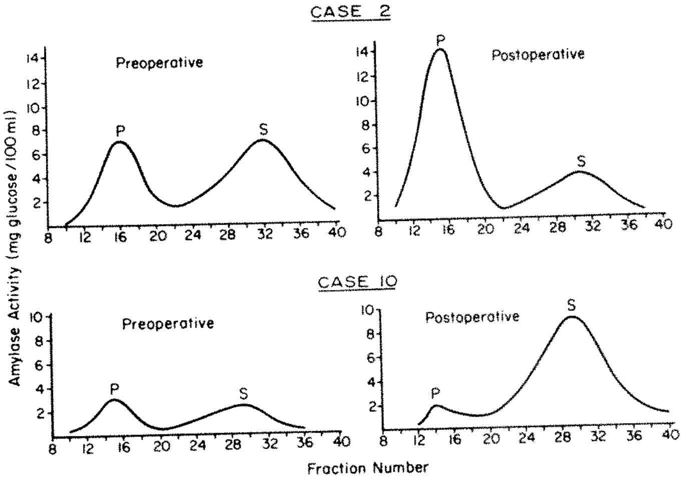

FIG. 1. Serum isoamylase patterns before and after operation. (Case 2) Elevation of P-type; (Case 10) Elevation of S-type.

pancreatitis following various operative procedures; in at least seven (10%) the procedures were clearly extra-abdominal procedures.

It has been generally assumed that elevation in serum amylase activity occurring postoperatively, even in the absence of signs and symptoms of pancreatitis, is the result of release of amylase from the pancreas. Harada, Kitamura, and Ikenaga,[11] however, have recently studied the isoamylase pattern in the sera of patients showing postoperative hyperamylasemia. Agar gel electrophoresis was used for this purpose. They found that of the 18 patients in their series who showed an increase in serum amylase activity after surgery, the rise in six was in pancreatic amylase. In the other 12 patients, the rise

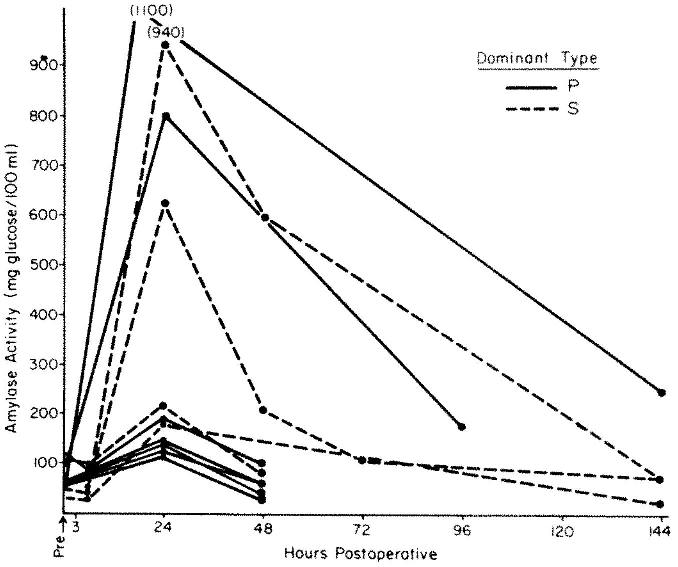

FIG. 2. Postoperative total serum amylase values in patients showing significant rise after operation. Also indicated is the isoamylase component principally affected.

was in an amylase component that displayed electrophoretic properties on agar gel identical to those of salivary amylase. Moreover, the most striking elevations were of this salivary-type amylase.

Our data confirm that postoperative hyperamylasemia in some cases may be due to an increase in salivary-type amylase. This finding may provide one explanation for those cases in which marked postoperative hyperamylasemia occurs without clinical evidence of pancreatitis. Our data also indicate that, excluding the two cases with abdominal operations during which the pancreas could have been affected (Cases 6, 7), the most striking rises in serum amylase activity were due to increases in the S-type isoamylase (Fig. 2 and Table 2).

Whether the S-type isoamylase originates solely from the salivary glands is not yet settled. Present evidence indicates that the salivary glands are clearly one source, and probably the principal source, of this isoamylase.[9] Amylase concentration in other organs with S-type isoamylase (liver and fallopian tubes), does not appear from our observations to be sufficient to make an appreciable contribution to the serum level.[9]

It is of interest that in every case in which the S-type isoamylase rose, there was an initial drop at 3 hours after surgery. Of note, too, was the observation that many of the patients studied demonstrated a slight drop in serum amylase levels at three hours with a return toward preoperative levels at 24 hours in most. This may reflect parasympatholytic effects of atropine administered preoperatively. The same mechanism might also explain the fall in serum amylase postoperatively in those patients whose levels were elevated preoperatively. It is conceivable as well that S-type hyperamylasemia may represent a rebound secretion by the salivary glands after the effects of atropine are dissipated.

Aside from the two cases in which surgical trauma to the pancreas could have occurred, and in which there was a pronounced rise in P-type isoamylase, it was not possible to establish any relationship between the type of postoperative isoamylase elevation and the nature of the surgical procedure. There was also no correlation with age, sex, pre- or postoperative medication, type of anesthesia, or receipt of blood.

Elevations of serum amylase occurring after upper abdominal operations have usually been explained by direct injury to the pancreas or pancreatic duct or to vascular impairment. Injury of the sphincter of Oddi by instrumentation has also been advanced as a pathogenetic factor. The consequence of such injury may be interruption of the flow of pancreatic secretion or reflux of duodenal contents.[22]

The pathogenesis of hyperamylasemia and pancreatitis following nonabdominal operations is much less readily explained. Morgan and his associates[16] found that the level of trypsin inhibitor in the pancreatic secretion of postoperative patients is decreased. They postulated that this may be a metabolic response to trauma and could occur following procedures removed from the area of the pancreas. The use of narcotics before, during, and after surgery may also be influential, since the serum amylase may rise following the administration of morphine and other analgesics.[3-5,17,21] There are still other factors involved with surgical procedures in general that could affect serum amylase activity. It is conceivable, for example, that a rise in S-type isoamylase may result from salivary gland injury when general anesthesia is administered and an endotracheal tube is inserted. Additionally, hyperamylasemia may represent a non-specific response mediated by stress-provoked mechanisms. Thus, Challis *et al.*[7] produced hyperamylasemia in dogs by the administration of adrenocorticotrophic hormone (ACTH). They suggested that the hyperamylasemia occurring in various pathological conditions may result from the spontaneous release of ACTH and activation of the adrenal cortex.

Isoproterenol and other catecholamines stimulate amylase secretion in the rat parotid glands,[6] probably through the mediation of cyclic AMP.[2] Adenyl cyclase in both the pancreas and parotid gland is stimulated by isoproterenol, but there is much less of this enzyme activity in pancreatic preparations. Parotid cyclic AMP levels are greatly increased after *in vivo* administration of isoproterenol in the mouse, whereas little change is observed in the pancreas.[15] Cellular or membrane functions may be altered and pancreatic macromolecular transport may be increased or decreased by certain chemical compounds. Illustrative of such actions are the observations of Singh *et al.*[20] using *in vitro* models. These investigators showed that streptomycin and lidocaine enhanced secretion of amylase, that atropine had no effect on basal secretion, and that tetracycline hydrochloride, amphotericin B, and valinomycin decreased secretion.

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Organ Specificity in Hyperacute Rejection of Canine Heart and Kidney Allografts

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To clarify the organ specific nature of hyperacute rejection, 14 puppies were presensitized by multiple skin grafts and spleen cell injections prior to receiving either a heart or kidney allograft from the respective donors. Of this group, 7 received orthotopic heart allografts and 7 received kidney allografts. All heart allografts were rejected between 3 and 28 hours, and all kidneys between 0 and 24 hours as judged by cessation of urine flow from the ureterostomies. In contrast, all 11 animals in a recent series of heart allografts in non-sensitized puppies survived the operation, and rejected between 7 and 17 days. There was a significant correlation in both groups between preoperative cytotoxic antibody titer in the recipient serum and graft survival time. The preoperative titers were all above 1:1,024 but were greatly reduced within 2 hours after transplantation. At the time of rejection, antibody could be eluted from the rejected organs. In contrast to the kidneys, in which 2 of 7 grafts ceased to function immediately after revascularization, all hearts resumed beating and functioned well for at least several hours. At autopsy, the myocardium was pale and edematous and histologically polymorphonuclear leukocytes were prevalent in and around the small vessels and among myofibers. Both IgG and IgM antibody was detected in sarcolemma of the myocardium and to a lesser extent in the intima and adventitia of the small vessels by the fluorescent antibody technique. Biopsies of the rejected kidneys showed polymorphonuclear leukocyte infiltration, typical of hyperacute rejection. Marked fluorescence of IgG and IgM in the glomeruli and peritubular capillaries was observed. This study indicates that both organs rejected hyperacutely in our experimental model and participation of the preformed antibody in effecting this change was strongly suggested.

WE HAVE PREVIOUSLY DESCRIBED an experimental model of orthotopic cardiac allotransplantation in which hyperacute rejection occurred consistently in the presence of high titer preformed cytotoxic antibody.[13] This phenomenon must be avoided in clinical heart transplantation, because of the drastic reaction that usually occurs as has been suggested by other investigators.[2,21]

The present study was designed to investigate the pathogenesis of hyperacute rejection of orthotopic cardiac allografts in comparison to that of renal allografts produced under similar experimental conditions. Special emphasis was placed on immunofluorescent and cytotoxic antibody studies.

Materials and Methods

Fourteen pairs of unrelated mongrel puppies of both sexes, weighing 3–5 kg, were prepared for presensitization using the most effective protocol derived from the previous investigation.[13] The initial sensitization was achieved with a 4 × 4 cm full-thickness skin graft transplanted from a potential heart or kidney donor followed by an intramuscular injection of spleen cells (1.0×10^9–5.4×10^9). The spleen cells were obtained by hemisplenectomy from the respective donor. Another series of skin and spleen cell injection was repeated alternately as the third and fourth procedures at approximately 2 week intervals. After completion of this protocol, seven puppies received orthotopic cardiac allografts and the remaining seven puppies received bilateral renal allografts from the respective donors.

The surgical procedure of orthotopic heart transplantation under profound hypothermia has been described in previous papers.[12,14] The heart grafts were transplanted by anatomosing both atria, the aorta, and the pulmonary artery under total circulatory arrest of the recipient animal. The electrocardiogram and femoral

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arterial pressure were monitored throughout the operative procedure and up to 2–4 hours after the operation.

Bilateral renal allotransplantation was performed as follows. The grafts were obtained by dissecting both kidneys with the segments of the abdominal aorta and vena cava in a block. The proximal stumps of these vessels were ligated, and heparinized lactated Ringer's solution (6–8 C) was irrigated from the distal stump of the aorta to flush out the blood. Side-to-end anastomosis with 5-0 Mersilene was made between the lower end of the host abdominal aorta and the distal stump of the graft aorta, and the lower end of the host inferior vena cava and the distal stump of the graft vena cava. The recipient was bilaterally nephrectomized immediately after transplantation. Condition of the grafts and urine flow from the ureters were monitored for 1 hour; then, if the grafts remained functional, the laparotomy was closed with two cutaneous ureterostomies in the lower abdomen. Since we did not encounter remarkable technical imperfections in this series, time of rejection was tentatively defined by the death of the animal in heart transplantation, and by cessation of the urine secretion from ureterostomies in kidney transplantation. Biopsy or autopsy was performed immediately thereafter for immunological and histological studies.

Sections for histologic study were fixed in 10% formalin and stained with hematoxylin-eosin.

Immunofluorescent Technique

Rabbit antidog-IgG and -IgM were prepared in our laboratory by the following methods. First, in order to increase the content of IgG and IgM in the canine serum, kidney allografting was performed on the dogs 7 to 9 days prior to exsanguination. Canine IgG and IgM, which were to be employed as antigens, were isolated from the serum by salting out twice with 50% saturated ammonium sulfate followed by gelfitration through a Sephadex G-200 column. The isolated IgG and IgM were purified by diethylaminoethyl (DEAE) cellulose column chromatography.[5] The purity of the IgG and IgM was determined immunoelectrophoretically against rabbit antidog serum (Cordis).

Then, approximately 1 mg of IgG or IgM in 1 ml volume was mixed with an equal part of complete Freund's adjuvant (Difco Laboratories, Detroit, Michigan). Five New Zealand white rabbits were immunized with the emulsion of IgG and five, with IgM by subcutaneous injection in foot pads and several parts of the back. The immunizations were repeated two more times at 3-week intervals in the same manner. Two or three weeks after the last immunization, the rabbits were exsanguinated.

To purify the sera, lipoproteins were precipitated with heparin and $MnCl_2$.[15] The lipoprotein-depleted serum

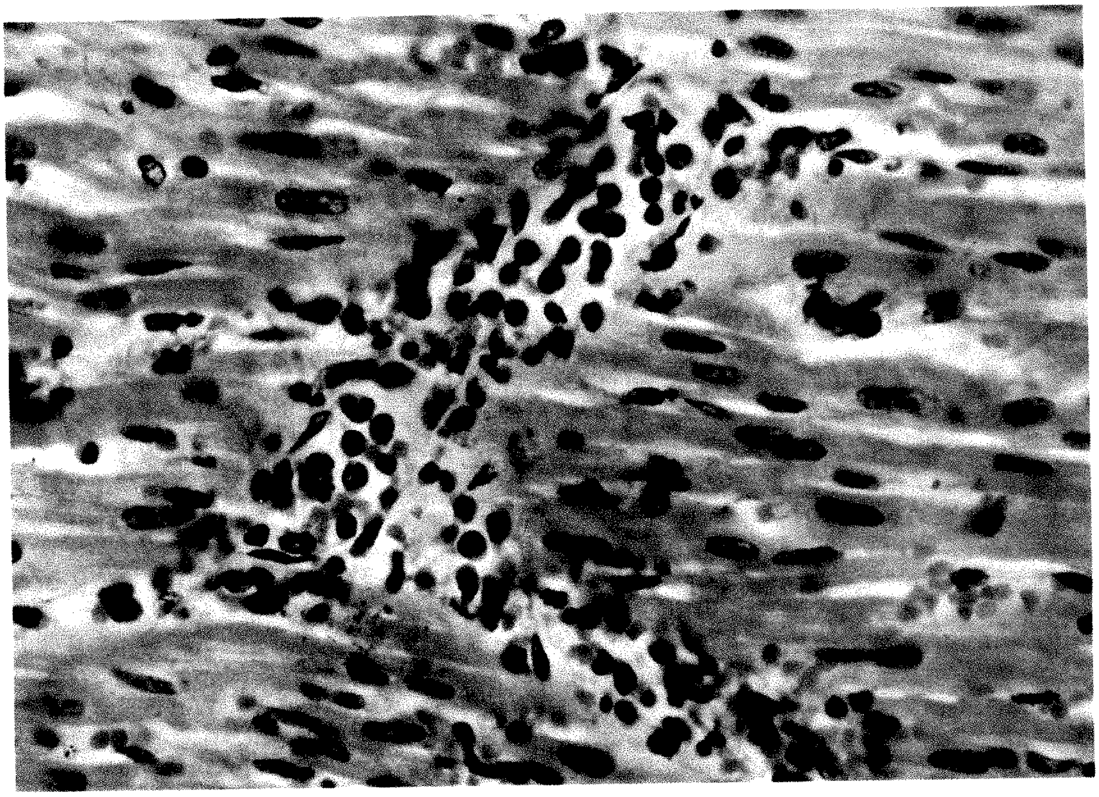

FIG. 1. Subendocardial myocardium from the heart rejected within 13 hours, demonstrating increased numbers of polymorphonuclear leukocytes in and around the small coronary vessels (Hematoxylin and eosin stain, ×130).

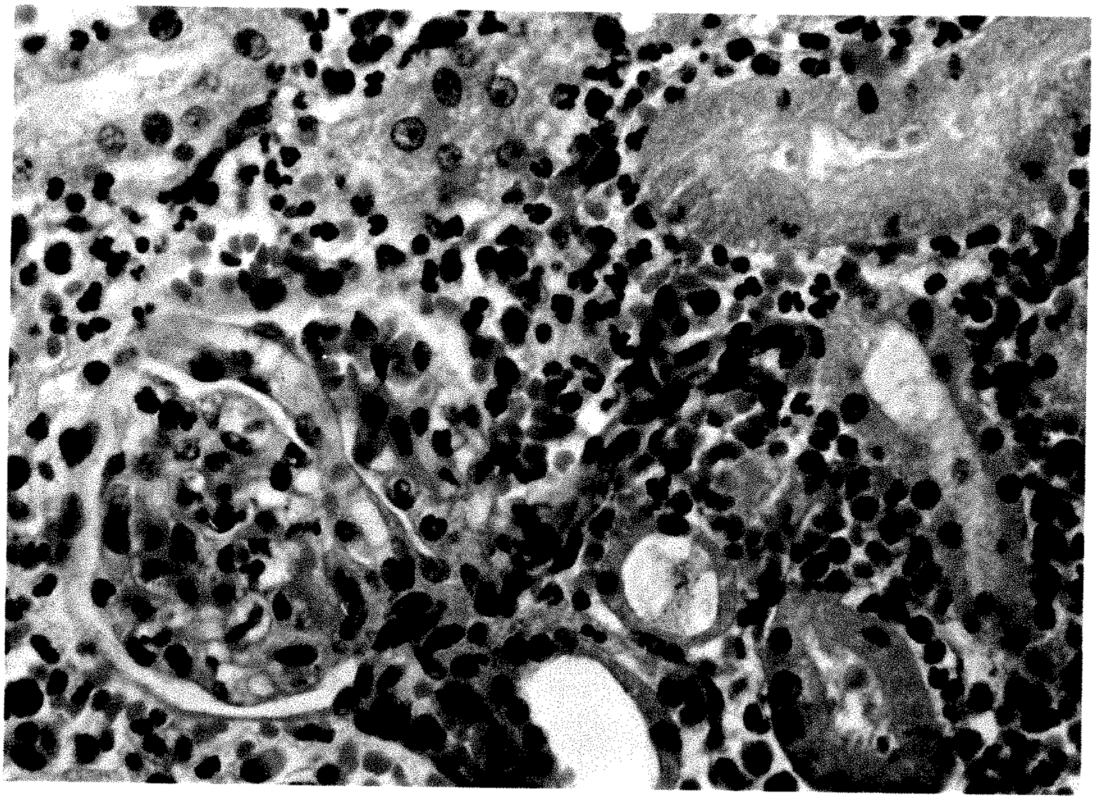

FIG. 2. Kidney graft rejected in hyperacute fashion within 7 hours, showing polymorphonuclear leukocyte accumulation in glomerular and peritubular capillaries (Hematoxylin and eosin stain, ×130).

was precipitated three times with ammonium sulfate at 33% saturation. The sediment was dissolved in phosphate buffered saline (PBS; pH 7.4) and, after removal of ammonium sulfate, the globulin was further purified by gelfiltration with Sephadex G-200 and DEAE cellulose chromatography. In order to reduce the cross reaction of IgG and IgM due to the common parts of the light chains, antidog-IgG and -IgM was absorbed with purified dog IgM and IgG respectively. Specificity of antidog-IgG and -IgM was examined by the Ouchterlony test and immunoelectrophoresis.

Purified anti-IgG and -IgM were labeled with fluorescein isothiocyanate (FITC) isomer 1 (crystallized BBL preparation) by the method of Kawamura.[8] Nonspecific staining activity of the labeled antibody was absorbed with acetone powder of mouse liver (Sylvania). The fraction with 1–2 molar ratio of fluorochrome to protein (F/P) was used for staining tissue sections.

Blocks of graft tissue obtained by biopsy or autopsy were frozen in n-hexane using a dry ice-acetone mixture or in liquid nitrogen and stored air-tight at less than

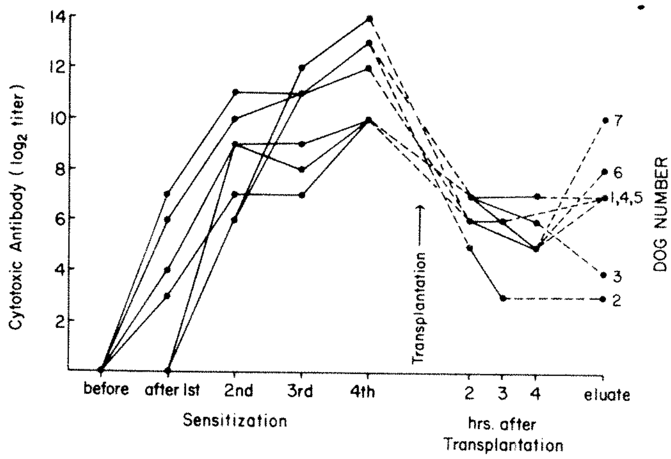

FIG. 3a. Changes in the titer of cytotoxic antibodies with heart or kidney (Fig. 3b.) allografts and leukoagglutinating antibodies with heart (Fig 3c.) or kidney (Fig. 3d.) allografts. Stepwise increase in titer through the sensitizations and abrupt drop after transplantation are clearly indicated in all figures. Eluate from the rejected grafts showed significantly high titer.

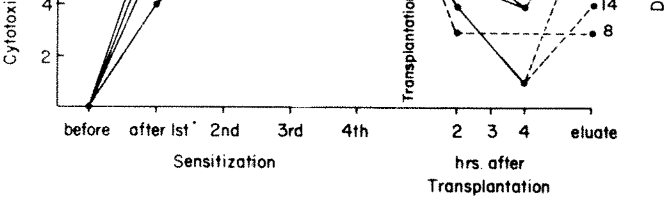

FIG. 3b.

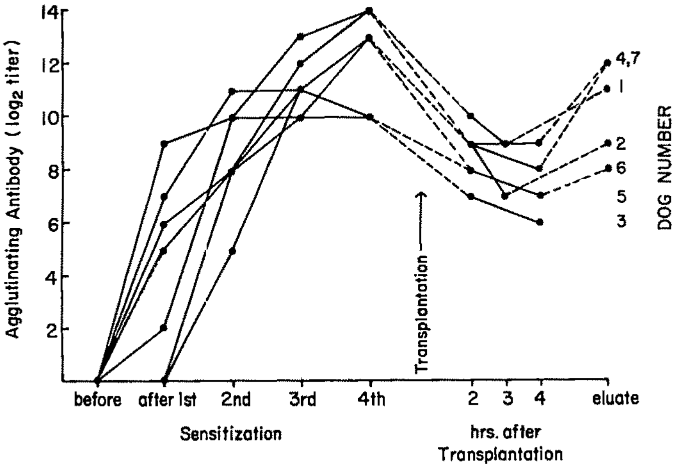

FIG. 3c.

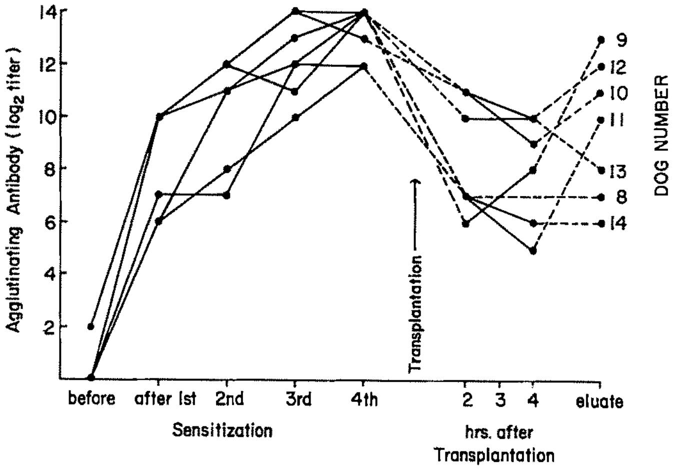

FIG. 3d.

−20 C. Cryostat sections 4 μ in thickness were airdried, washed in PBS for 10 minutes and used without fixing. Staining with the labeled anti-IgG or anti-IgM antibody was performed at 37 C for 30 minutes followed by washing with PBS for 2 hours and rinsing with distilled water. The sections were mounted in carbonate buffered glycerol and were examined on the same day. They were observed and photographed using an Olympus Universal Research Microscope Model VANOX with a FITC filter, an immersion dark field condenser, and a halogen lamp as a light source.

Cytotoxic and Leukoagglutinating Antibody Tests

Panels of test sera were prepared from peripheral blood of the potential recipients harvested just prior to each presensitization procedure, prior to transplantation, and 2 and 4 hours after transplantation. Eluates of the rejected grafts prepared by the method of Klassen and Milgrom[10] were included in the panels. The lymphocyte suspensions were prepared from heparinized donor blood using a Ficoll-Hypaque gradient isolation system.[18,20] Cytotoxic antibody tests were performed using the microtechniques described by Epstein[4] with minor modifications. One drop of lymphocyte suspension, one drop of rabbit complement (Hyland), and one drop of serial double-fold antiserum dilutions were mixed in a microtiter plate and incubated at 37 C for 60 minutes. After mixing with two drops of 0.25% solution of trypan blue in TC Hanks, the percentage of blue stained cells was counted. Cytotoxic antibody titer was defined as the highest dilution of antiserum which killed greater than 25% of the cells. The leukoagglutination test was performed using the technique of Dausset *et al.*[3]

Results

The 7 heart allografts were rejected between 3 and 28 hours and the 7 kidney allografts from immediate to 24 hours. In contrast, all 11 animals in a recent series of heart allografts[13] in non-sensitized puppies survived the operations and remained active and healthy until cardiac rejection occurred on from the 7th to the 17th day (mean, 11.7 days). One puppy of the present allograft group, which stood up, ate food and drank water the next morning, died at 28 hours of typical accelerated rejection. All hearts resumed beating and blood pressure was maintained sufficiently with or without minimal norepinephrine infusion. They awoke from anesthesia in a few hours, but in most instances remained lethargic. In two cases, regular heart beat was obtained spontaneously after cardiac massage for several minutes. However, the myocardium of the other animals appeared cyanotic, and repeated electric shocks were required to defibrillate the hearts. Generally, resuscitation of the

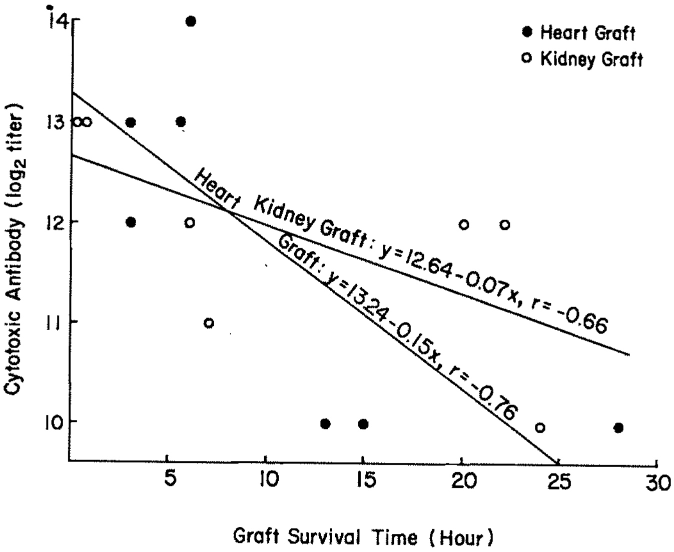

FIG. 4. Correlation between cytotoxic antibody titer and graft survival time.

TABLE 1. *Survival Time and Immunofluorescent Antibody Study on Heart Allografts in Presensitized Puppies*

Dog No.	Graft Survival Time (hours)	Immunofluorescence IgM Vessel	IgM Sarcolemma	IgM Interstitium	IgG Vessel	IgG Sarcolemma	IgG Interstitium
1	3	++	++	−	++	++	−
2	3	+++	++	+	+++	+++	+
3	5½	++	++	+	++	++	+
4	6	++	+++	+	++	+++	+
5	13	++	++	+	++	+++	+
6	15	+	++	−	++	+++	+
7	28	++	+	+	+	++	+

Immunofluorescence was divided into 4 classes: +++, severe; ++, moderate; +, mild; and −, absent.

hearts in presensitized recipients was much more difficult than has been experienced in non-sensitized puppies. Two of seven kidney allografts ceased urine production shortly after revascularization; the remaining five allografts, between 6 and 24 hours after transplantation.

Histopathology

Autopsy revealed no technical imperfections to explain the early failure of the heart and kidney. Five hearts rejected within 13 hours appeared normal in size, although the right ventricle was usually distended. The myocardium was cyanotic, and contained scattered areas of subepicardial hemorrhage. This lesion could be attributed in part to surgical trauma, since subendocardial hemorrhage was rare. The lungs and abdominal organs revealed mild congestion. A distinct feature of these heart grafts was an increased number of polymorphonuclear leukocytes in some of the capillaries and perivascular areas. (Fig. 1). Some were arranged chain-like in a bloodless capillary, suggesting damage to the intima.

The hearts rejected at 15 and 28 hours demonstrated more definite pathology. The chest cavities contained an enlarged heart with slightly hemorrhagic exudate. The myocardium was dusky-red, rubbery and edematous with foci of hemorrhage. Histologic findings in the myocardium included mild mononuclear and polymorphonuclear leukocyte infiltration, interstitial edema, and hemorrhage.

Two kidney grafts, which were rejected almost immediately after restoration of blood flow, were characterized by mottling and cyanotic appearance, loss of turgor, cessation of urine excretion, and poor bleeding from the biopsy sites. The paired kidneys of a graft showed essentially the same attributes. Microscopically, there was an increased number of polymorphonuclear leukocytes within glomerular and peritubular capillaries (Fig. 2). The tubular epithelium revealed unremarkable changes.

The remaining five kidney grafts, rejected between 6 and 24 hours, showed severe congestion, swelling, and hemorrhage. After obtaining the open biopsy, four of them were left *in situ* until 24 to 48 hours after transplantation. All of them resembled grossly the ultimate rejection seen in unmodified renal allografts. Severe interstitial hemorrhage, congestion, probable tubular degeneration, and cellular infiltration, predominantly with polymorphonuclear cells were the uniform findings.

Cytotoxic and Leukoagglutinating Antibody Studies

As shown in Fig. 3, cytotoxic and leukoagglutinating antibody titers increased after each sensitizing procedure and all the puppies had titers above 1:1,024 at the time of grafting. Within 2 to 4 hours after grafting, the cyto-

TABLE 2. *Survival Time and Immunofluorescent Antibody Study on Kidney Allografts in Presensitized Puppies*

Dog No.	Graft Survival Time (hours)	Immunofluorescence IgM Vessel	IgM Glomerulus	IgM Tubulus	IgG Vessel	IgG Glomerulus	IgG Tubulus
8	0	++	+++	+	++	+++	+
9	0	+	++	+	+	++	+
10	6	++	+++	+	++	+++	+
11	7	+	++	+	+	++	+
12	20	+	++	+	++	++	+
13	22	+	++	+	+	++	+
14	24	++	++	+	++	++	+

Immunofluorescence was divided into 4 classes: +++, severe; ++, moderate; +, mild; and −, absent.

toxic antibody titers were reduced to 1:128 or lower, and the leukoagglutinin titer to 1:1,028 or lower. Cytotoxic and leukoagglutinating antibody could be eluted in significantly high titer from the rejected heart muscle and kidney parenchyma (Fig. 3). There appeared to be a correlation in both groups between preoperative cytotoxic antibody titer in the recipient serum and graft survival time. The correlation coefficient was −0.76 in the group of heart grafts and −0.66 in the group of kidney grafts (Fig. 4).

Immunofluorescent Antibody Studies

The results of immunofluorescent studies in the rejected organ are summarized in Tables 1 and 2. There was intense fluorescence for IgG and IgM in the sarcolemma of the myocardium, but no specific fluorescence was found in the sarcoplasma. Therefore, microscopic observation of the transverse section revealed a honeycomb pattern (Fig. 5). Some capillaries in the myocardium showed strong fluorescence, although this finding was not consistent. Moderate deposition of IgG and less intensity of IgM were demonstrated in the perivascular connective tissue and intima of the small coronary arteries and veins. No fluorescence was detected in the large coronary vessels. In some cases, fluorescence positive mononuclear cells were seen sporadically in the vessels or myocardium.

In the rejected kidney grafts, there was marked fluorescence of IgG and IgM in the glomeruli and moderate fluorescence in the intima and adventitia of the small vessels (Fig. 6). Peritubular capillaries were also stained weakly with fluorescent antibodies. As a general rule, no clear difference was elucidated between the localization of IgG and IgM antibody. The specificity of the reaction was confirmed when fluorescence was blocked by pretreatment with unlabeled antidog-IgG and -IgM reagents.

Discussion

The method of presensitization of the recipient animal with the multiple skin grafts and spleen cell injections was very effective. All animals sensitized in this way revealed stepwise increases of donor specific lymphocytotoxic antibody titer with a final value of 1:1,024 or

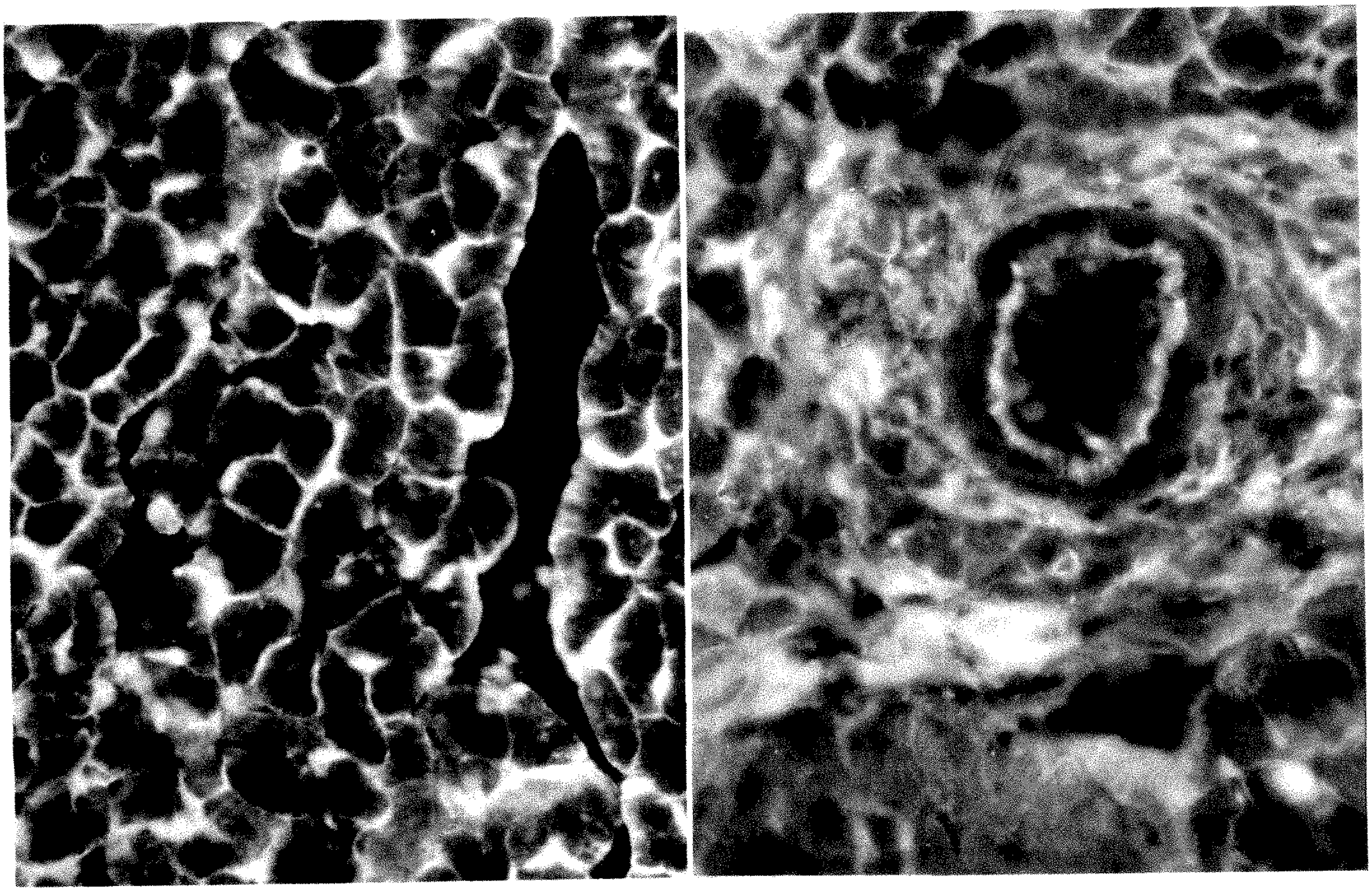

FIG. 5. The heart stained with fluorescent labeled anti-IgG reagent. (Left) Rejected after 6 hours. Note intense fluorescence in the sarcolemma of the myocardium (×130). (Right) Rejected after 13 hours. IgG accumulation around the small coronary vessels and in the sarcolemma (×130).

higher. Leukoagglutinating antibody titers also showed a parallel change. All of the kidney grafts and six of the seven heart grafts were rejected within 24 hours.

In our previous experiments,[13] we could not define a correlation between the titer of donor specific serum antibody in the recipient and the survival time of the grafted heart. Several other investigators working in the area of hyperacute rejection also failed to observe any correlation.[1,7,16] However, the present data suggest that there is a good correlation between the survival time of the heart or kidney grafts and the cytotoxic antibody titer in the pretransplant recipient serum. This discrepancy may be related to improvements in presensitization procedure and technical differences in cytotoxic antibody test. Mullerworth *et al.*[17] found a similar correlation between rejection time of the heterotopic cardiac allografts and the serum antibody titer in the dog. The rapid decline in serum antibody titer following transplantation and the presence of antibody in the eluate of rejected organs again support our previous assumption that antibody is absorbed selectively by the graft tissue.

Using immunofluorescent techniques, several investigators[6,17,19] detected IgG on the sarcolemma of cardiac allografts in various phases of rejection including the hyperacute, accelerated and acute rejection. No IgG was detected in sarcoplasma, although Heron[7] indicated the intracellular deposition of γ-globulin in degenerated myofibers. This study clearly demonstrated sarcolemmal IgG and IgM in the hyperacutely rejected myocardium. We could not detect fluorescence in the sarcoplasma. Because of the limitation of the method, we could not find the correlation between the intensity or localization of the fluorescence on the sarcolemma and the time of rejection. Existence of fluorescence in the wall of small vessels, as observed in this study, was also recognized by Mullerworth *et al.*[17] However, in the present study large coronary vessels showed no fluorescence and this observation was in contrast to the report by Heron[7] in heterotopic rabbit heart allografts; γ-globu-

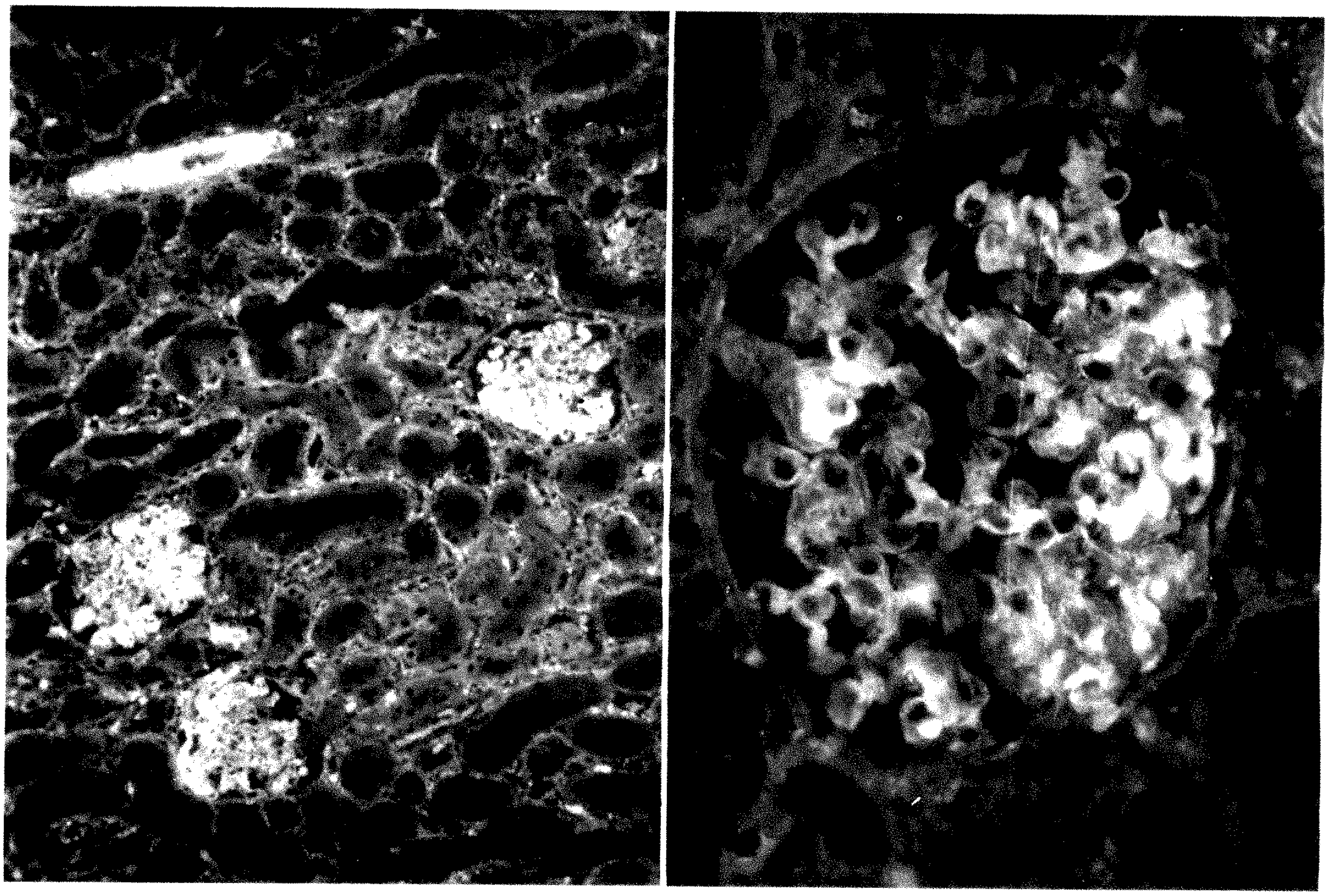

FIG. 6. The kidney stained with fluorescent labeled anti-IgG reagent. (Left) Rejected after 6 hours. Marked fluorescence of IgG in the glomeruli and moderate fluorescence in the intima and adventitia of the small vessel (×130). (Right) Rejected after 6 hours. Irregular accumulation of IgG in the glomerulus (×130).

lin was bound to the intima, and incorporated into the media and adventitia of some large vessels. In the orthotopic heart allografts, changes observed at the time of cessation of function are milder than those observed in the heterotopic allografts, in which coronary flow of the graft is maintained by host cardiac performance beyond the stage of functional end point. Although fluorescent positive mononuclear cells were seen, their character and function were not pursued.

In the rejected kidney grafts, fluorescence of IgG and IgM observed in the glomeruli was most marked in the glomerular capillaries. The intensity was variable among the glomeruli both in the same section and between the areas in the same glomerulus. Peritubular fluorescence was weaker than that of the glomeruli. These findings suggest that dysfunction of the kidney in the course of the hyperacute rejection process occurs due to the deterioration of glomerular function. Comparing the hyperacute rejection of heart and kidney grafts, there was a notable difference in the time of rejection. Two of seven kidneys were rejected almost immediately after restoration of blood flow. Such vigorous immediate rejection of the heart has not been observed in our experience. Williams *et al.*[21] and Kissmeyer-Nielsen *et al.*[9] reported cases of human renal allotransplantation which were rejected hyperacutely within 1 hour. MacDonald *et al.*[16] and Kobayashi *et al.*[11] have reported immediate rejection after revascularization of canine renal allotransplantation. No instance of hyperacute rejection in clinical heart transplantation has been reported, although an accelerated type of rejection has been described.[2,21] Although we do not have definite knowledge to explain these differences, we can assume that the vasculature of the kidney is more sensitive to immunologic insult than is the heart, and that the candidates for renal transplantation have more opportunity to presensitize through repeated hemodialysis.

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Fetus-in-Fetu:

An Unusual Cause for Abdominal Mass in Infancy

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Fetus-in-fetu is an unusual cause of retroperitoneal abdominal mass in infants, which most likely arises from inclusion of a monozygotic, diamniotic twin. This entity is distinguished from teratoma by its embryological origin, its unusual location in the retroperitoneal space, its invariable benignity, and by the presence of vertebral organization with limb buds and well-developed organ systems. Diagnosis is made radiographically by the finding of a diminutive vertebral column on a plain abdominal film. The treatment of choice is total excision with special attention being given to the fetus' blood supply which may be directly from the host's superior mesenteric vessels. A well-documented example of this unusual entity that occurred in a six-week old infant male is presented.

FETUS-IN-FETU is a rare cause of abdominal mass in infancy which should be carefully differentiated from the more common, retroperitoneal teratoma. The distinction between these entities has been a subject of considerable controversy. The purpose of this report is to present evidence that fetus-in-fetu is an unusual aberation of monozygotic twinning; whereas, teratoma is an embryonic neoplasm with distinct malignant potential.

Case Report

A 6-week-old, white male was referred to the James Whitcomb Riley Hospital for Children on 12/20/72 with an abdominal mass. The infant was a product of a full term pregnancy and weighed 6 lbs, 14 oz at birth. Labor was of two hours duration and delivery was uneventful. The baby's Apgar scores at one and five minutes were both 10. The mother was a 22-year-old, gravida-2, para-2, and abortus-0. There was no history of twinning or teratomas in either parents' families. In the neonatal period, the infant was completely asymptomatic and showed a normal growth and developmental pattern. At six weeks of age, during a routine pediatric examination, a right-sided abdominal mass was palpated and the child was referred for evaluation. On admission, the infant appeared healthy and in no acute distress. He weighed 9 lbs, 15 oz and the blood pressure was 85/60, pulse rate 120/min, respiratory rate was 30/min and temperature was 98.6 F. Significant physical findings were limited to the abdomen. On the right side, a large, round, firm, and fixed mass was easily palpable. It extended from the upper flank to the linea alba and down to the iliac crest. It was nontender and did not transilluminate. The abdomen was not obviously distended. Bowel sounds were normal and rectal examination was unremarkable. Chest x-ray was normal. Erect, recumbent and lateral, plain abdominal x-rays demonstrated bone densities consistent with a well organized fetal spine in the right abdomen (Fig. 1). Well-formed long bone densities were also observed. These findings were considered diagnostic of fetus-in-fetu. The hemoglobin was 9.9gm, hematocrit was 28%, and white blood cell count was 11,700/mm^3 with 15% polymorphonuclear leukocytes, 80% lymphocytes, 4% monocytes, and 1% eosinophiles. Urinalysis, blood urea nitrogen, and serum electrolyte values were normal. A coagulation profile showed the prothrombin time, partial thromboplastin time, and fibrinogen level to be normal. Peripheral blood smear demonstrated a microcytic hypochromic anemia typical of iorn deficiency. Urinary chorionic gonadotropins were normal. Twenty-four hour urinalysis for 17-ketosteroids and 17-hydroxy-corticosteroids were also within the normal range.

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Supported by HEW Maternal and Child Health Project #924 and awards from the John A. Hartford Foundation, Ind., and the James Whitcomb Riley Memorial Association.

Reprint requests: Jay L. Grosfeld, M.D., James Whitcomb Riley Hospital for Children, 1100 West Michigan Street, Indianapolis, Indiana 46202.

Operative Findings

An operation was performed through a large transverse supra-umbilical incision. The ascending colon, cecum and appendix were stretched over a large right retroperitoneal mass. The right kidney was displaced anteromedially and the mass was in intimate contact with the under surface of the liver and posterior retroperitoneum. After dividing the peritoneal attachments, a firm retroperitoneal mass enveloped by a semi-transparent sac-like capsule was encountered. This was mobilized down to a stalk that entered the paravertebral musculature adjacent to the upper lumbar vertebra near the base of the mesentery. The capsule was incised and a bi-lobed feti-form structure was noted. The umbilical cord was contiguous with this stalk. When the stalk was severed to remove the sac and fetus, arterial bleeding was encountered. These vessels were appropriately suture ligated. The vascular stalk did not appear to anastamose with any of the surrounding mesenteric vessels. The mass was removed en-toto and the abdomen closed in layers in the usual fashion. The postoperative course was uneventful and the patient was discharged on the seventh postoperative day. One month later, the boy weighed 10 lbs, 2 oz and was in good health. Six months postoperatively, the infant continued in good health and weighed 16 lbs, 8 oz.

Pathological Examination

Gross examination of the fetus showed it to be anencephalic. Two upper limb buds were noted (Fig. 2). Finger-like projections were seen coming off the superior limb buds. A patent omphalomesenteric duct was noted and the fetus was taken to the X-ray Department where a contrast study of the bowel demonstrated relatively well-developed bowel in what appeared to be the mid-gut (Fig. 3). The bowel contained soft green, inspissated material. A spleen, pancreas, and adrenal gland were also identified. The lower part of the fetus demonstrated lower limb buds and radiographically showed a boney pelvis. Each lower limb bud showed a primitive femur, tibia, fistula, and primitive foot and phalanges. Hair was noted on the back of the inferior segment. There was an imperforate anus and is was obvious that the hind-gut had not fully developed. A complete vertebral column was present. A small area with what appeared to be brain tissue was also identified.

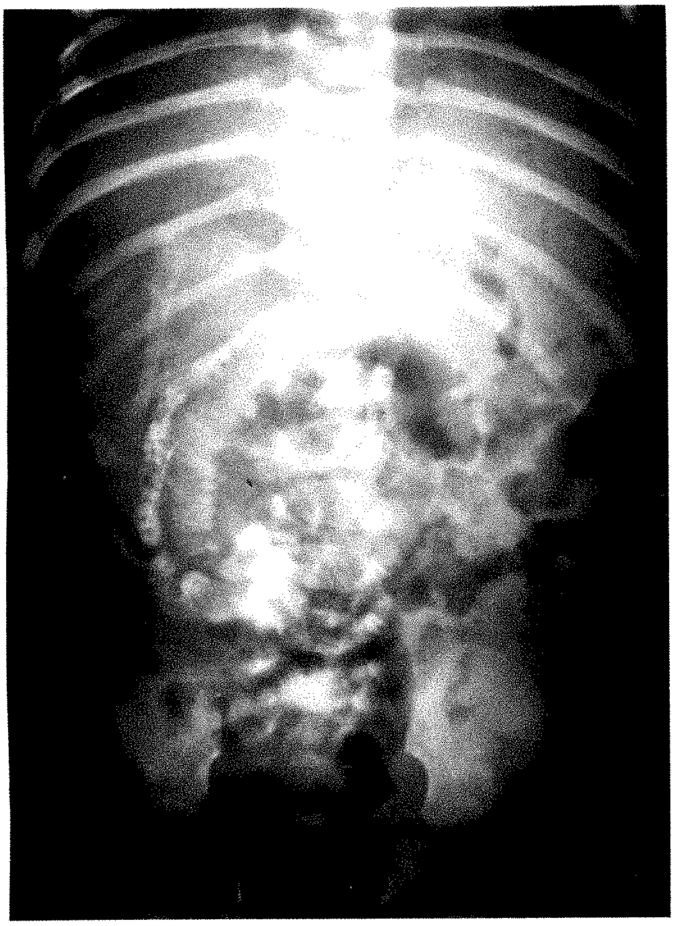

FIG. 1. Abdominal radiograph demonstrating the presence of the vertebral column and long bones of the included fetus-in-fetu.

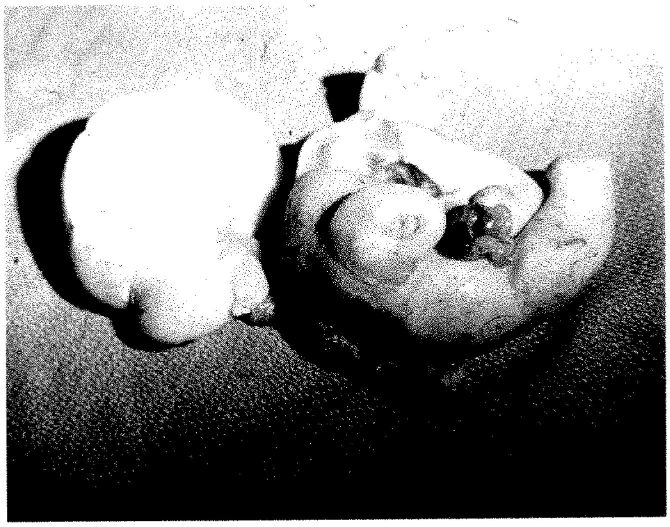

FIG. 2. Photograph of the specimen showing the fetus-in-fetu to be anencephalic. Limb buds are apparent as well as a patent omphalomesenteric duct.

Microscopic evaluation demonstrated normal histological features of jejunum, ileum and proximal colon. A small fragment of pelvic tissue resembling primitive prostatic acini among fibromuscular stroma was also noted. Skin sections showed hyperkeratosis with follicular plugging. Large numbers of hair follicles, sweat glands, and sebaceous glands were seen in the dermis. The gastroduodenal region and adjacent pancreatic tissue containing acini and islet cells were identified. The adrenal gland demonstrated normal cortex and a few medullary cells. The vertebral column showed irregular cartilagenous arches of focal bone formation. The bone marrow showed active hematopoesis. A few ganglia, nerve segments, and some pigment bearing choroid were identified. In the central canal of the vertebral area, neuroglial tissue containing nerve cells and ependymal lining was found. Nerve roots and telangectasis of local capillaries were seen. Sections of the skull and brain showed highly vascular nervous tissue including glial areas, astrocytes, ependymal lining, meninges and a well-formed choroid plexus.

Genetic Studies

Chromosome studies were performed on fibroblasts cultured from the fetus and on leukocytes and fibroblasts from the normal infant. Both subjects had a 46 XY karyotype with no evidence of mosaicism. Staining of the preparations with quinacrine mustard revealed heteromorphic flourescent markers on chromosome #3 and #21 in both preparations. C-banding showed no other polymorphic variants. Histo-compatibility typing was performed on

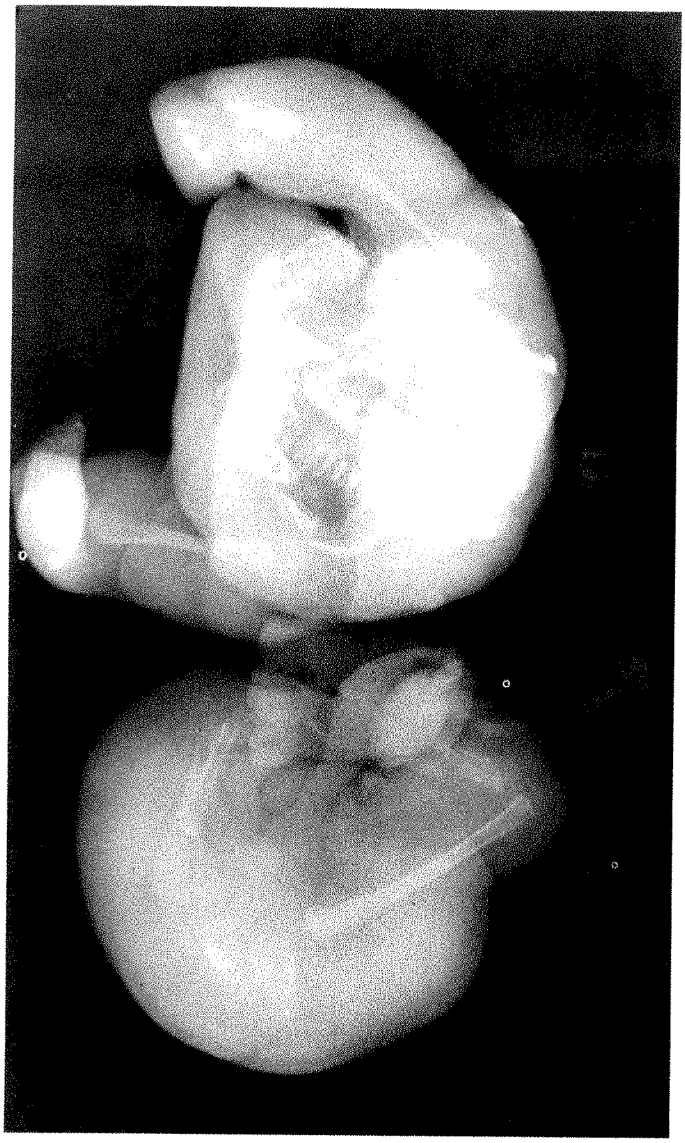

FIG. 3. Contrast study of the primitive gut, obtained by injection of dilute barium through the patent omphalomesenteric duct. Skeletal structures can also be seen.

cultured fibroblasts from the infant and fetus using a technique developed by Krieger and Biegel.[1] Both fibroblast lines demonstrated the HL-AL and W19 antigens at the first sublocus and the HL-A5 and HL-A2 antigens at the second sublocus.

Discussion

The great majority of abdominal masses in the newborn are of renal origin. Wedge *et al.*[16] found hydronephrosis and multicystic kidney to be the most common causes with enterogenous duplication and genital (ovarian cysts or hydrocolpos) lesions occurring less frequently. Neuroblastoma is the most common neoplasm in the neonate.

Teratomas rarely arise in the retroperitoneal area in the neonate and account for less than 5% of retroperitoneal masses in all age groups. Retroperitoneal teratomas, however, are far more common than fetus-in-fetu. Teratomas may also occur in the anterior mediastinum, testes, ovary, liver, cervical, presacral, and sacrococcygeal regions.

The distinction between fetus-in-fetu and teratomas has been a subject of considerable controversy. Willis believed that the two conditions could be clearly resolved by clinical and pathologic criteria.[17] He regarded teratomas as a discordant congregation of pluripotential cells that demonstrate no vertebrate segmentation or systematic organogenesis. Lacking a primary organizer, embryonic tissues that compose a teratoma cannot pass through an organized primitive streak stage which endows the developing organism with its fundamental vertebrate pattern. In addition, teratomas occur in many extraretroperitoneal locations and have definite malignant potential. In contrast, Lord[14] observed that the fetus-in-fetu is almost always retroperitoneal in location, is benign in nature, and possesses a vertebral skeleton and often an appropriate arrangement of other organs and limbs with respect to this skeletal axis. The present case meets all of the accepted criteria for a fetus-in-fetu. As in other well documented cases, reported by Lord,[14] Gross and Clatworthy,[5] Janovski[8] and Farris and Bishop,[1] the fetus was located in the retroperitoneal area, had a basic vertebral column, and in addition had anatomic, radiographic and histologic evidence of other well-developed organ systems.

A recent report by Kakizoe and Tahara[9] described a fetus-in-fetu in the scrotal sac of a full term Japanese infant. This unusual location suggests migration of the fetus along with normal descent of the testes from the retroperitoneal area to the scrotal sac. Kimmel *et al.*[10] reported a case in which multiple fetal masses were found in the cranial cavity of a hydrocephalic infant. Since not all of the fetal masses had organized axial skeletons, the validity of this finding as an infallible criteria for distinguishing teratomas from fetus-in-fetu is open to question. Because of this uncertainty and the similar histologic findings, some authors, such as Lewis[12] and Warkany[15] have questioned whether a clear distinction can be made between the two conditions. Recent observations, however, and the findings in the present case suggest that fetus-in-fetu and teratomas may have quite different embryological origins.

Fetus-in-fetu is widely believed to represent an aberration of monozygotic twinning in which the parasitic fetus becomes included in the autosite (host). Genetic and cytogenetic studies, however, have previously been performed only in the case described by Grant and Pearn.[4] In their report, the typing results of the fetus and host were identical for eight blood group systems. Chromosome studies revealed an XY karyotype in both subjects, but a structural variation in the short arm of an A group chromosome was noted in the fetus but not the host. In the present case, sufficient blood could not be obtained from the fetus for genotyping. Monozygosity, however, is supported by the finding of identical histocompatibility types and identical male karyotypes which, on detailed analysis with chromosomal banding techniques, were found to include two normal polymorphic marker chromosomes.

In contrast to the origin of fetus-in-fetu, Linder and Power have recently provided compelling genetic evidence for the parthenogenic (reproduction by development of an unfertilized gamete) origin of ovarian teratomas from post-meiotic germinal cells of the host.[13] These authors found that tumors derived from patients who were heterozygous for genetically determined enzyme variants frequently showed expression of only one of the two genes and concluded that the tumors must have been derived from cells in which meiotic segregation had occurred. Whether a similar mechanism is applicable teratomas in males or to non-gonadal teratomas is uncertain. In the present case, the host and fetus were identical and heterozygous for histocompatibility type, and two chromosomal markers. In addition, both possessed a single X and Y chromosome and could not have arisen from a single post meiotic cell. Thus, the available genetic evidence clearly indicates that fetus-in-fetu differs from some teratomas in its embryologic origin. Whether all teratomas are pathogenically homogeneous remains uncertain.

Certain teratomas, most notably those of the sacrococcygeal area, are known to occur more frequently in twins and are associated with a family history of twinning.[6] Early sex chromatin studies of teratomas suggested that they were often discordant with the chromosomal sex of the patient.[7] More recent data, however, employing karyotype analysis have not shown such striking differences.[3]

The present instance and previous reports demonstrate fetus-in-fetu to be an axial vertebrate organism with limb buds and various stages of development and organ system differentiation. The majority of the specimens are anencephalic, with some cases showing evidence of cranial bone anlage and neural tissue. This suggests that caudal growth from the primitive streak procedes in a relatively normal manner; however, cephalad growth from Henson's node is inhibited.

Janovski described a Japanese boy in whom a 2.0 cm tumor was noted at age three months.[8] No treatment was given. At five years of age, the tumor had increased in size but caused no symptoms. At laparotomy, a retroperitoneal fetus-in-fetu with its blood supply derived from two branches of the superior mesenteric artery was found. The mass was excised, however, the patient died of retroperitoneal hemorrhage and pulmonary complications. Gross and Clatworthy[5] described a case of twin fetus-in-fetu in which one obtained its blood supply from the base of the mesentery where its vessels communicated with the superior mesenteric artery and vein. In the present case, we could not grossly demonstrate any communication to the superior mesenteric vessels. An angiogram, which might have been more informative, was not performed. Careful control of the blood supply to the fetus-in-fetu, however, is of obvious importance. In four of the eight cases reviewed by Lord, there was a vascular network between the fetus and host.[41] In agreement with previous reports, however, no true placental tissue was observed on histologic examination in the present case. The absence of a functioning placenta was confirmed by the infant's normal urinary chorionic gonadotropin levels prior to surgery.

While most cases have been diagnosed in young infants, Galatius-Jensen *et al.* and Himore (as quoted by Lord) reported instances in teenagers 17- and 15-years-old, respectively.[2,14] Of further interest is an article from the Sunday Chicago Tribune (November 3, 1922) which reported a case of fetus-in-fetu from the medical examiner's office in Springfield, Massachusetts. This was observed during an autopsy of an aged man killed by an automobile. A male infant weighing five or six pounds, fully formed, with the exception of the head, was found in the abdomen. The baby within the abdomen had one arm slightly shriveled, but the other was nearly perfect as was the remainder of the body.

The diagnosis of fetus-in-fetu is based simply on the observation of a vertebral column in an abdominal mass on plain abdominal x-ray. The treatment of choice for fetus-in-fetu is operative removal. The key points in the procedure are adequate transperitoneal exposure and careful control of the vascular supply to the fetus which may be derived from the superior mesenteric artery. Operative excision should be done to confirm a benign diagnosis and to obviate the potential effects of continued compression on surrounding structures, as well as the danger of infection, infarction, or hemorrhage. Regarding the latter, Himore's case (as described by Lord) demonstrated hemorrhage and rupture of the sac wall of the included fetus into the gastrointestinal tract of a child who ultimately died.[14]

Acknowledgments

We gratefully acknowledge the aid of D. Krieger and A. Biegel in performing the HLA-typing.

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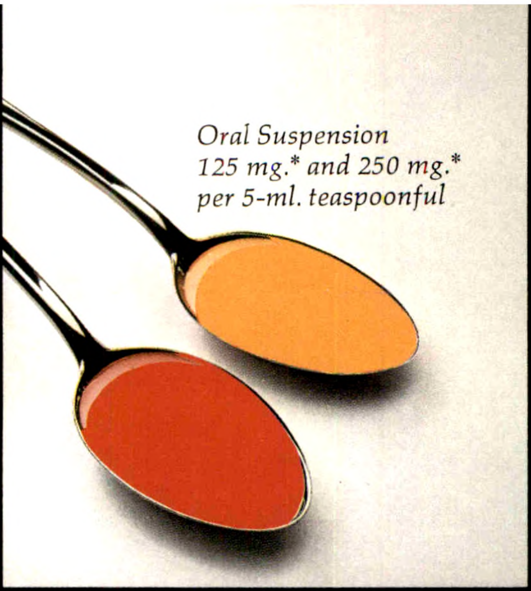

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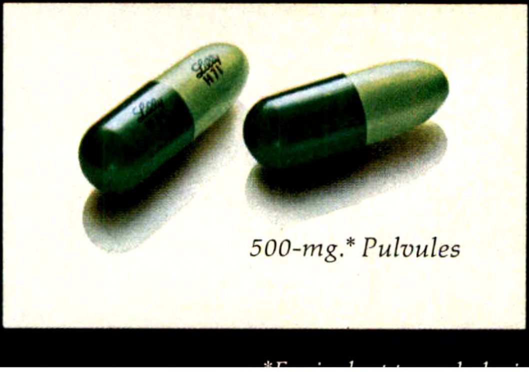

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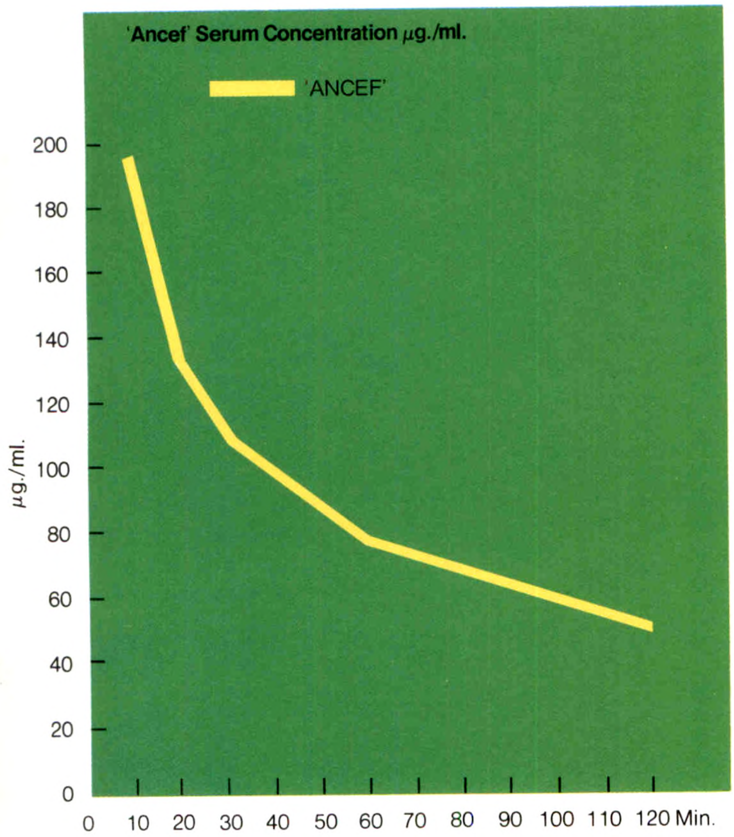

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'ANCEF' Indications

Respiratory tract infections due to *D. pneumoniae, Klebsiella* species, *H. influenzae, S. aureus* and group A beta-hemolytic streptococci.

Genitourinary tract infections due to *E. coli, P. mirabilis, Klebsiella* species and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *S. aureus*, group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *S. aureus*.

Septicemia due to *D. pneumoniae, S. aureus, P. mirabilis, E. coli* and *Klebsiella* species.

Endocarditis due to *S. aureus* and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

'ANCEF' I.V. has a low risk of phlebitis at the injection site.

Duration of I.V. Therapy	Number of Patients	Average Daily Dose	Number with Phlebitis
1 day or less	13	3.0 g.	1
2 days	43	2.6 g.	1
3 days	31	3.3 g.	1
4 days	19	2.6 g.	1
5 days	37	2.6 g.	1
6 days	26	4.7 g.	0
7 days	26	3.8 g.	0
8 days	17	3.0 g.	0
9 days	11	3.1 g.	0
10 days	6	2.7 g.	0
More than 10 days	44	4.9 g.	1
Total	273	3.4 g.	6 (2.2%)

Of 273 patients receiving 'Ancef' intravenously, 6 patients or 2.2% reported phlebitis at the injection site. As can be seen in the above chart, which presents the duration of I.V. therapy, average daily dose and the occurrence of phlebitis, most cases of phlebitis occurred in the first few days of therapy which may be indicative that the inflammation was caused by the mechanical trauma of setting up the I.V. rather than continuing irritation of the drug itself.

These data were derived from pre-marketing clinical studies in small populations. Further clinical experience may reveal a greater incidence of adverse effects.

Pain on injection is infrequent with 'Ancef'.

ANCEF® Has Produced No Nephrotoxicity in Extensive Clinical Trials.

(Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.)

Adverse Reactions.

Adverse reactions reported in the clinical trials included: pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of adverse reactions associated with 'Ancef' therapy, please see brief summary of prescribing information on next page.

See following page for a brief summary of prescribing information including contraindications, warnings, precautions and dosage.

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DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Diplococcus pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus.*

Septicemia due to *Diplococcus pneumoniae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'ANCEF' IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for mild gram-positive infections is 250 mg. to 500 mg. of 'Ancef' every 8 hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every 8 hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 gram of 'Ancef every 6 to 8 hours. 'Ancef' has been administered in dosages of six grams per day in serious infections such as endocarditis. 'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.) 60% of the normal daily dose given in divided doses q12h should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.) 25% of the normal daily dose given in divided doses q12h should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.) 10% of the normal daily dose given q24h should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dose may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef® (sterile cefazolin sodium, SK&F) — supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

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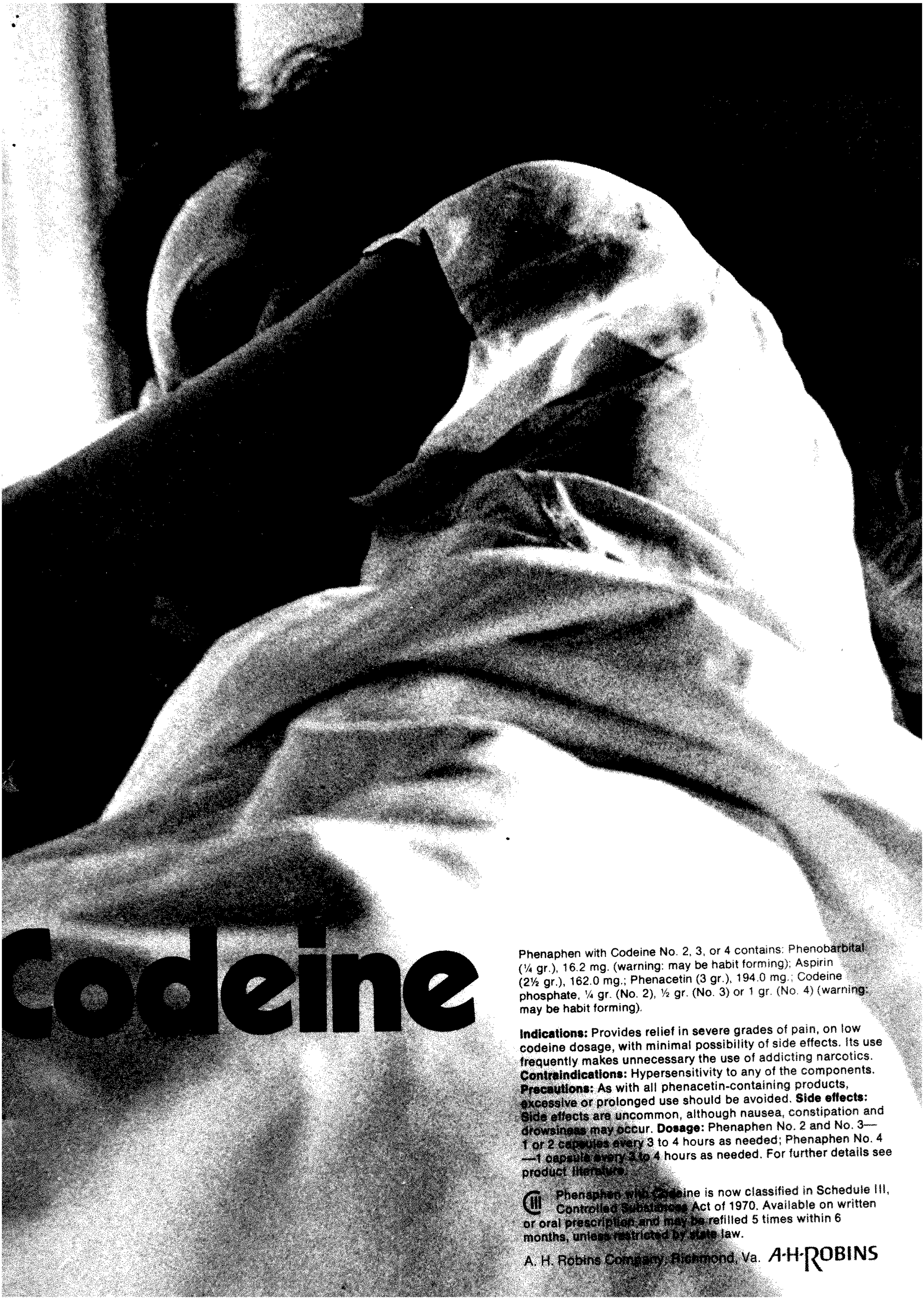

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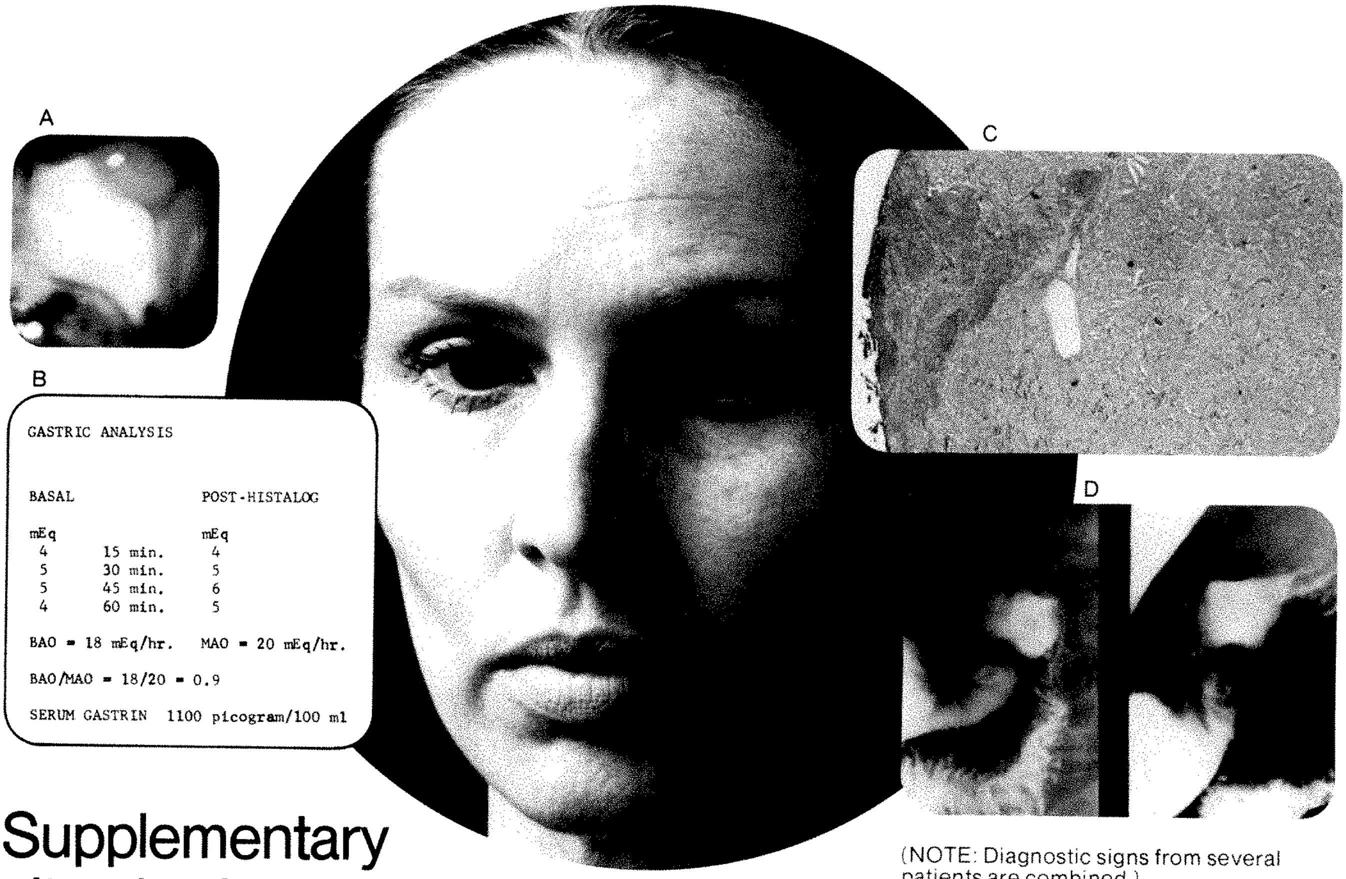

```
GASTRIC ANALYSIS

BASAL                    POST-HISTALOG

mEq                      mEq
 4       15 min.          4
 5       30 min.          5
 5       45 min.          6
 4       60 min.          5

BAO = 18 mEq/hr.    MAO = 20 mEq/hr.

BAO/MAO = 18/20 = 0.9

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(NOTE: Diagnostic signs from several patients are combined.)

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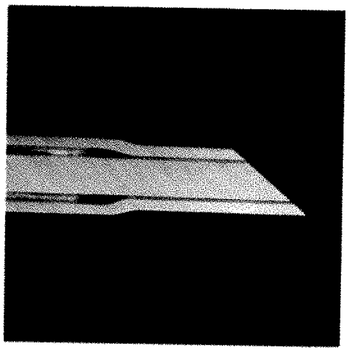

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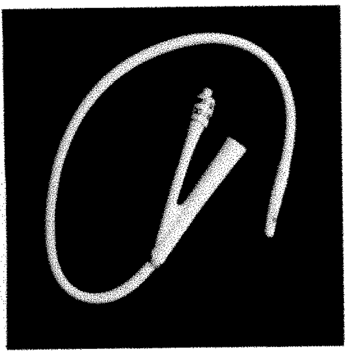

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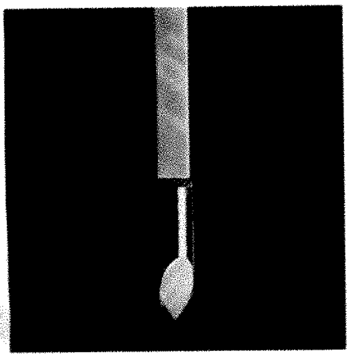

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Surgical nutrition—a case history: giant esophageal diverticulum; surgical treatment followed by esophagocutaneous fistula

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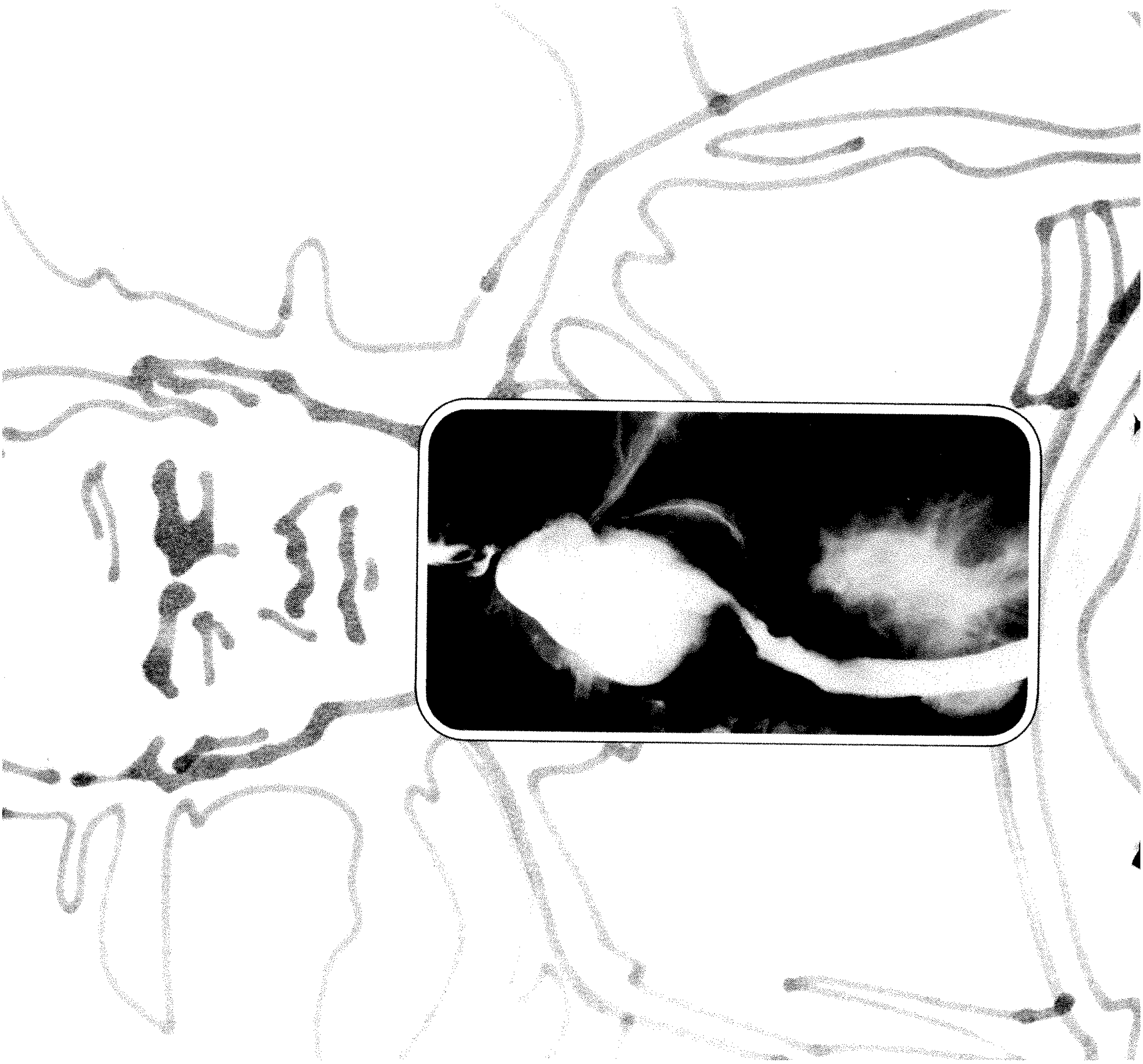
The patient: A 72-year-old man with a history of severe dysphagia was admitted to the hospital because his complaint had become markedly worse in the past few months. He could hardly swallow and regurgitated a considerable portion of what he did manage to eat. Thin almost to the point of emaciation, he was 68 inches tall and weighed 126 pounds. The patient was well below his desirable weight.

X-ray studies showed a massive cricopharyngeal diverticulum, extending down to the level of the aortic arch. No other abnormal conditions were found.

Surgical treatment: At operation the opening at the back of the esophagus was found to be about 2 inches in diameter. Extremely dense adhesions surrounded the diverticulum, and resection was accomplished only with



considerable difficulty. The excised tissue showed evidence of chronic inflammation, but no tumor was seen. A Levin tube was threaded through the esophagus under direct vision, and a Penrose drain was placed in the incision. The patient withstood the procedure very well.

Postsurgical course: For 3 days following the surgery, the wound seemed to heal normally; the patient was swallowing well, and his condition improved daily. However, when the Penrose drain was removed, an inflamed fistulous tract was discovered in the wound. An antibiotic and streptokinase-streptodornase were administered. Drainage from this opening continued for about 10 days.

Nutritional management: Inability to eat had caused deterioration of the patient's nutritional status as evidenced by gross weight loss. To provide for an optimal nutritional condition to meet increased postsurgical metabolic needs, Vivonex High Nitrogen was used and clear liquids were given as desired. Postoperatively, the patient experienced no weight loss. His nutritional status was greatly improved.

Outcome: Surgical results were good as demonstrated through regained normal function of the esophagus. With the aid of drug therapy, the postsurgical fistula closed spontaneously. When discharged the patient was in excellent condition, nutritionally stable, able to take a full diet and rapidly regaining weight.

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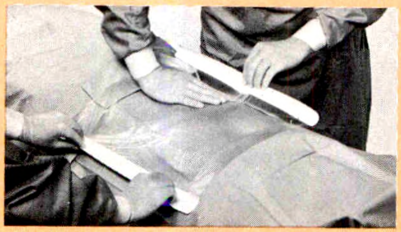

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Acute Hemorrhagic Pancreatitis and Pseudocyst Due to Mumps

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CHARLES A. KALLICK, M.D.,[‡] ALEXANDER DOOLAS, M.D., F.A.C.S.[§]

From the Departments of Surgery and Pediatrics,
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Hospital, Chicago, Illinois 60612

This is the first reported case of mumps hemorrhagic pancreatitis in a child, documented at operation, and by rising mumps titers and complicated by a pseudocyst. In severe cases when surgery is indicated, drainage of the lesser sac usually prevents pseudocyst formation. If a pseudocyst occurs, drainage is required to eliminate disabling pain and chronic pancreatitis. Live attenuated mumps vaccine may eliminate this source of pancreatitis from American children in the future.

HEMORRHAGIC PANCREATITIS and pseudocyst formation have on rare occasions been suspected to follow mumps, but never proven conclusively.[8] The refinement of viral isolation and serologic techniques[8] has made the diagnosis of mumps more certain, but has never been employed in the reported cases of pancreatitis believed to be caused by mumps. We present here the first reported case of mumps hemorrhagic pancreatitis in a child, documented at operation and rising mumps titers, and complicated by a pseudocyst.

Case Report

N.L., 881792, a four-year-old black male was brought to the emergency room on 12-24-68. He was unresponsive, cold, cyanotic, and the blood pressure was unobtainable. Vital signs were as follows: pulse 92/min, temp 39 C rect., and respirations 42/min. The abdomen was flaccid. Laboratory values were as follows: Hb 11.0 gm, Hct 32%, Na 147 mEq/L, K 4.5 mEq/L, Cl 111 mEq/L, BUN 29 Mg.%, FBS 150 mg %, pH 7.15, pO_2 108 mm Hg, SAT 95.5%. A spinal tap was nondiagnostic. The pH was corrected and the patient was transferred to the pediatric intensive care unit.

At this time a history obtained from the parents revealed that 2 days prior to admission, the child had complained of vague epigastric pain and had been given aspirin. He woke the night of admission again, complaining of abdominal pain and was sent to bed with aspirin. The next morning he was found limp and unresponsive, and was brought to the hospital. The child had been exposed to an older sibling who had mumps parotitis. It was then noted the patient had slight bilateral parotid swelling (Fig. 1).

Over the next 36 hours, the abdomen became more tender and distended (Fig. 2). The bowel sounds were high pitched and a foul smelling diarrhea followed. A flat plate of the abdomen revealed a "sentinel loop" of distended bowel[6] and a diffuse haziness (Fig. 3). His temperature rose to 39.5 C rectally. The FBS rose to 306 mg %, the serum amylase was 680 units, and the calcium was 7.1 mg %. Another amylase was 816 units and a diagnostic abdominal tap revealed sanguinous fluid with an amylase of 7,600 units. There were no bowel sounds at this time.

Because of severe abdominal distention impairing respiration, and because of the possibility of a surgical abdominal catastrophe, the patient was operated upon at noon of the second hospital day. A midline incision was made and 2,000 cc of serosanguinous fluid was drained. The omentum and mesentery exhibited diffuse areas of necrosis, saponification, and hemorrhage (Fig. 4). The pancreas was necrotic, hemorrhagic and grossly edematous (Fig. 5). Drains were placed in the lesser sac and the abdomen closed with retention sutures (Fig. 6).

The patient recovered remarkably until the eighth postoperative day when he pulled out his drains. He developed a tender 9 × 8 cm epigastric mass accompanied by a serum amylase of 1,125 units. A flat plate of the abdomen showed

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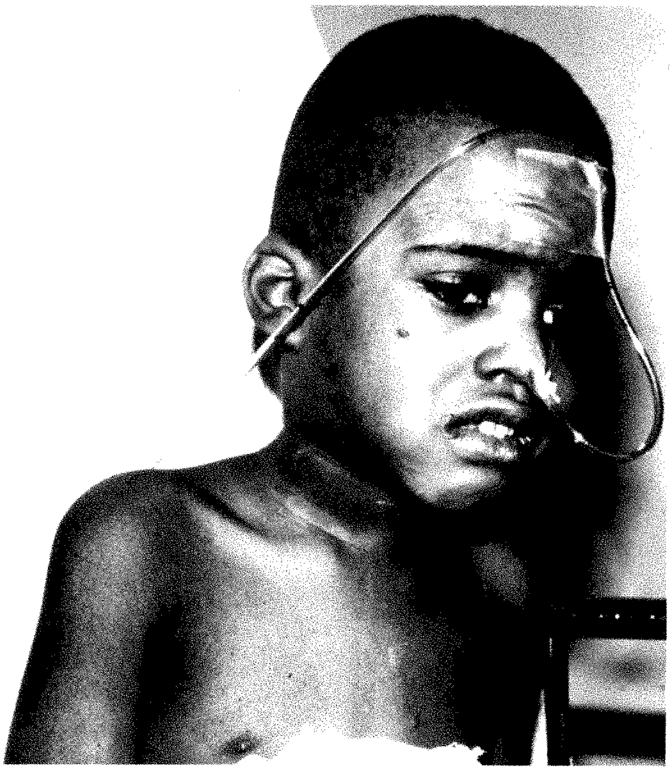

Fig. 1. Slight protuberance of parotid gland from mumps.

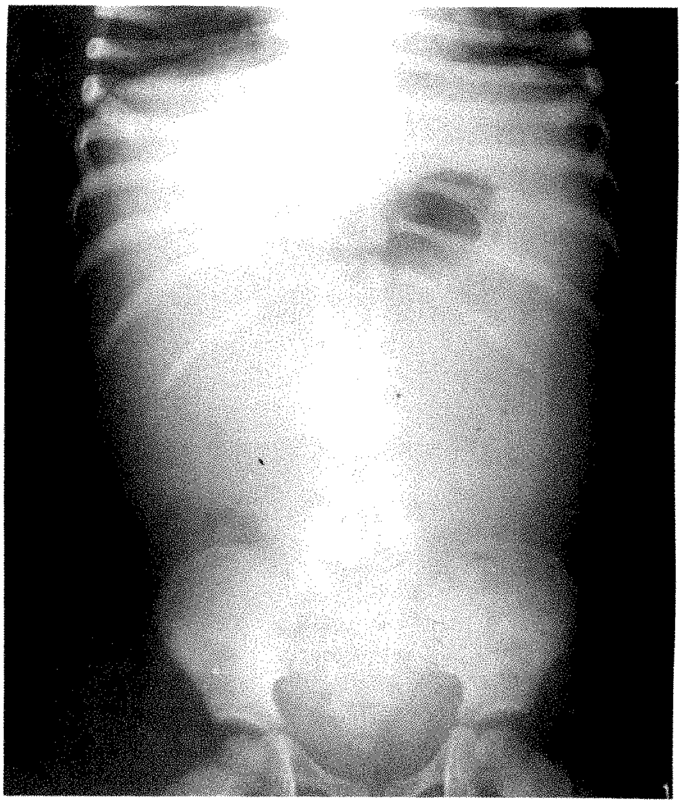

Fig. 3. Plain film showing abdominal diffuse haziness from ascites with sentinel loop of jejunum present.

anterior and superior displacement of the stomach (Fig. 7). An Upper G. I. Series supported the diagnosis of a pancreatic pseudocyst. The patient was re-explored and a large pancreatic pseudocyst was drained into a jejunal roux-en-y loop. The child did well and was discharged 6 days later. He remained asymptomatic for 4 months, but has since been lost to followup.

The acute phase mumps titers were as follows: soluble 1:8, virus 1:8. The convalascing mumps titers, taken at weekly intervals, were as follows: 1) soluble 1:16, virus 1:8; 2) soluble 1:16, virus 1:32; and 3) soluble 1:16, virus 1:32. A four-fold increase in the virus titer is indicative of recent mumps infection.

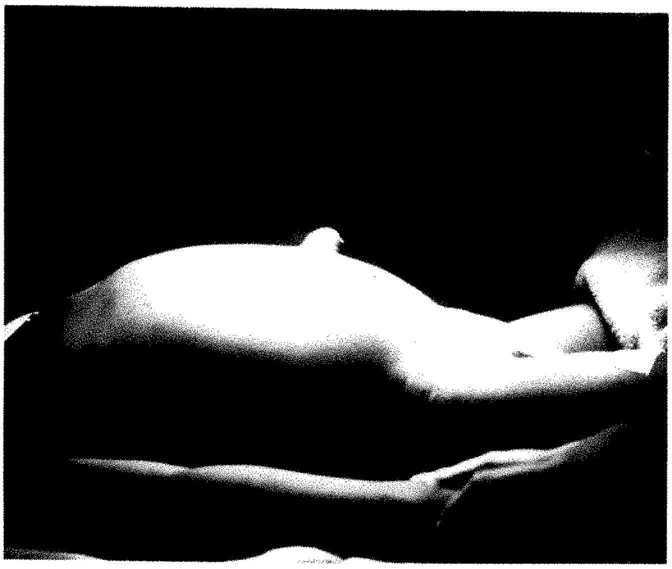

Fig. 2. Severe abdominal distention and protrusion of umbilical hernia. Abdominal distention compromised breathing.

Discussion

We report the first documented case of acute hemorrhagic mumps pancreatitis and pseudocyst formation, demonstrated by surgery, and by rising mumps titers. The clues leading to the diagnosis of our patient was a

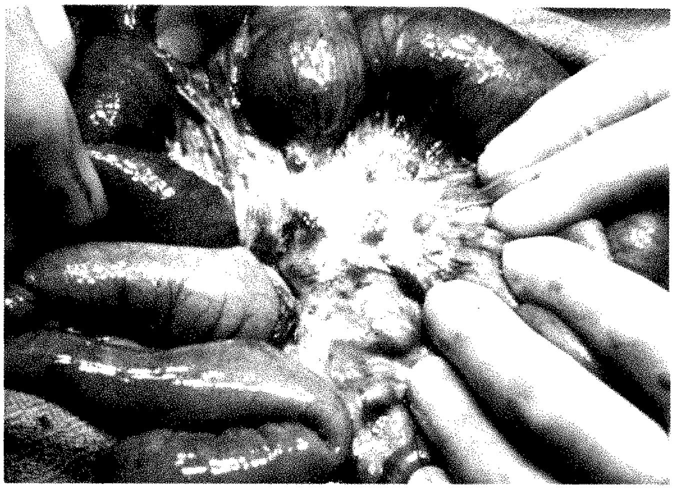

Fig. 4. Photograph of enlarged lymph nodes and calcification of mesentery from saponification.

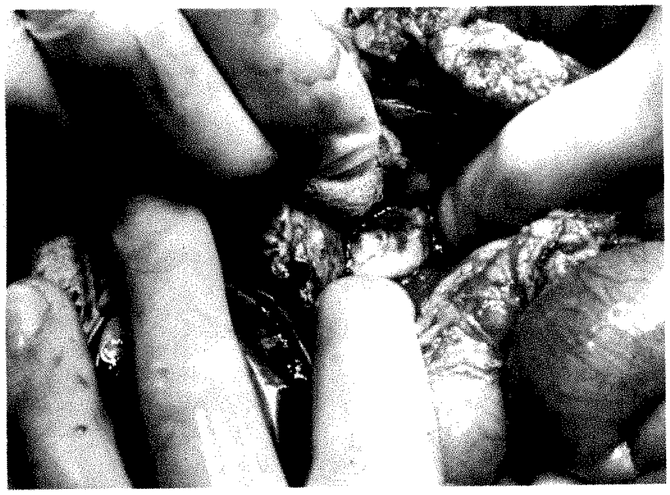

FIG. 5. Edematous pancreas seen through the lesser sac between stomach and colon.

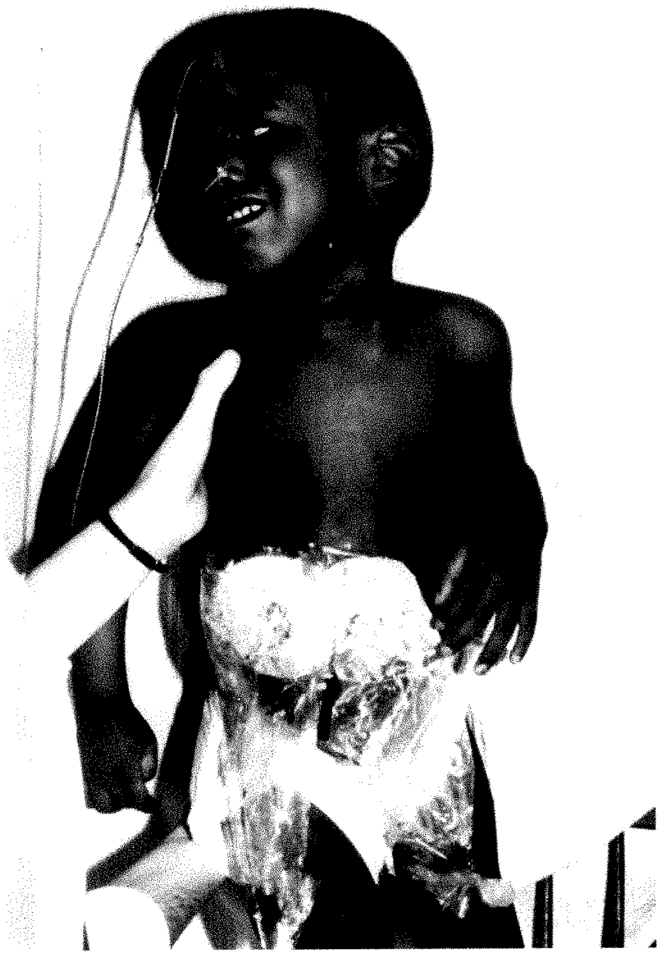

FIG. 6. Patient shown 12 hours postoperatively. He was walking and breathing better. Drainage bag shows serosanguinous fluid from lesser sac.

history of exposure to mumps and slight parotid swelling.

The pancreas is usually involved 3 to 5 days after the salivary glands, and may be the only organ clinically affected. Hemorrhagic pancreatitis was reported to be seen at surgery in a 22-month-old child whose sibling developed the disease 2 days later. The child however had no other physical signs of mumps and viral titers were not obtained.[2]

Such an association between pancreatitis and mumps in children has been restricted to single reports, or necropsy studies. An excellent review of pancreatitis in childhood was published in 1965 and hinted that the condition may be more common than previously supposed.[4]

The signs and symptoms of pancreatitis are common to both adults and children. The onset of the disease is of an abrupt nature with severe constant abdominal pain localized either in the periumbilical or epigastric areas and lasting from a few hours to several days. Shock, tachypnea, fever, nausea, and vomiting are usually present. There may be diarrhea or constipation and in rare instances the stools are bulky and fatty. Polyuria, glycosuria, hyperglycemia and leukocytosis are common findings. The abdomen is usually tender, rigid, silent,

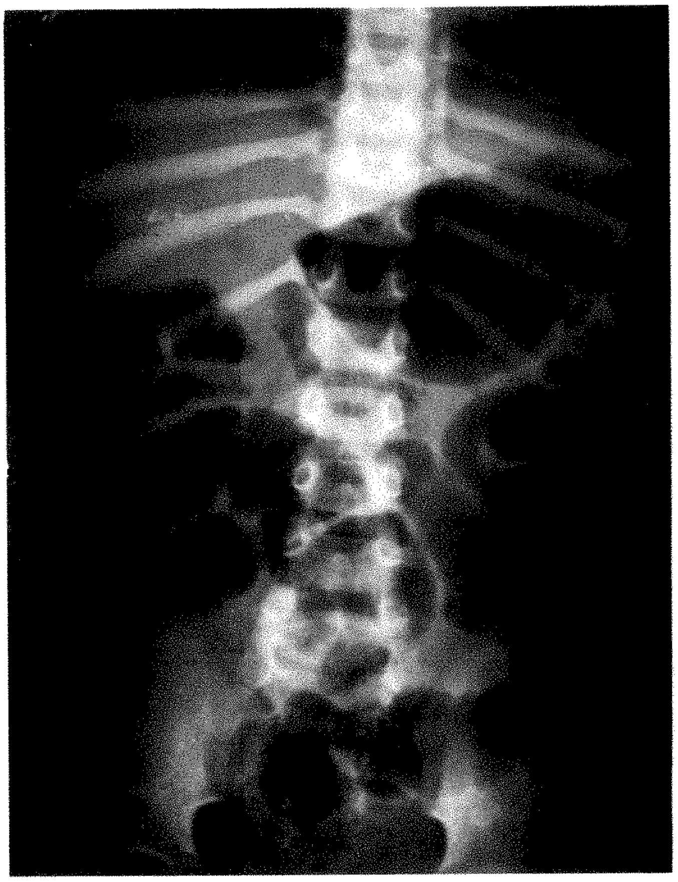

FIG. 7. Plain film of the abdomen showing stomach displacement anterior and superior from pseudocyst.

and distended with ascitic fluid. An elevated serum and urine amylase render the diagnosis extremely likely.

Surgery is indicated when other catastrophic abdominal conditions are suspected, or if the patient's condition deteriorates.

Pseudocyst can follow acute or chronic pancreatitis and is common in adults. The usual cause in children is trauma often leading to chronic relapsing pancreatitis.[7] Two cases were attributed to mumps but were not documented by titers.[5]

Since a reliable live attenuated mumps vaccine has been marketed for immunizing primarily school age children, mumps infection may become unusual in childhood, and severe cases may disappear in the United States.[1]

Acknowledgment

The authors wish to express their appreciation to Miss Ann Lobdell for her secretarial assistance in the preparation of this paper.

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Blood Flow During Obstruction to the Venous Effect of Portacaval Transposition on Hepatic Outflow from the Canine Liver

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University of Liverpool, Liverpool, England

When portacaval transposition (PCT) was performed in dogs in combination with a complete hepatic venous outflow block (COB) procedure, estimated hepatic blood flow (EHBF) declined steadily. Four weeks after this combined procedure mean flow was only 46% of the value obtained 3 days after operation, but this did not prevent the development of ascites which occurs in dogs with COB alone. Complete reversal of portal flow was demonstrated in the longest surviving dog. When PCT was performed in dogs with established partial outflow block EHBF remained at preoperative levels whether portal hypertension was present or not prior to the second operation. This maintenance of hepatic blood flow was due to continuing venous flow into the portal bed. It would appear that PCT is probably of little value as a treatment for portal hypertension and bleeding oesophageal varices in cases of advanced cirrhosis, but may be of some benefit in a few selected cases where the hepatic lesion is less severe.

THE SURGICAL TREATMENT OF PATIENTS with portal hypertension and bleeding oesophageal varices continues to present a problem. Although the various types of portacaval shunt (PCS) are usually successful in preventing further bleeding the depression of liver function after these operations often leads to hepatic failure and/or neuropsychiatric disorders.[7,10,24,25] These potentially fatal sequelae are almost certainly related to the diversion of portal blood and the consequent reduction in blood flow to the liver.[13,22]

A more satisfactory procedure would seem to be one in which hepatic blood flow is maintained whilst the splanchnic circulation was being decompressed. Thus the varices may be selectively decompressed by distal splenorenal shunt.[31] This operation is currently being assessed but it seems likely that it can be performed in only certain selected patients.[31]

An alternative procedure is portacaval transposition (PCT) introduced by Child and his colleagues[4] in studies aimed at evaluating the importance of portal blood on liver regeneration. Venous blood flow to the liver was maintained by anastomosing the inferior vena cava (IVC) to the hepatic end of the divided portal vein. Subsequently PCT has been performed with some success in children with glycogen storage disease.[23,27,28] Experimental work in dogs with relatively moderate cirrhosis induced by carbon tetrachloride has shown that hepatic blood flow is maintained at preoperative levels after PCT in contrast to the reduction after PCS.[8] However, in these animals the preoperative blood flow to the liver was normal and so the value of PCT in the treatment of patients with cirrhosis and portal hypertension, where the lesion is usually advanced, remains uncertain.

One of the most characteristic features of the human cirrhotic liver is obstruction to the hepatic venous outflow.[3,6,11,21,30] An experimental counterpart of this lesion can be produced in the dog by ligation and division of the right hepatic veins and gradual constriction of the large left hepatic vein (LVH).[16] This preparation has been used to study the effects of PCS,[18] and would seem to provide a useful model of an advanced hepatic lesion for assessment of PCT.

A study of the effect of PCT on hepatic blood flow in dogs with different degrees of outflow block of the liver

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was therefore undertaken, and a preliminary report has been presented.[1]

Methods

Operative Procedure

Dogs weighing 16–35 kg were anaesthetised with Halothane and the right hepatic veins ligated and divided as described by Orloff *et al.*[16] The LHV was then catheterised as previously described[2] to allow serial sampling of hepatic venous blood. The procedure was then continued in one of three ways as outlined below.

Group 1 (COB). In 19 dogs a casein plastic disc with a segment removed (ameroid constrictor) was placed around the LHV[29] which eventually becomes completely constricted. This group was therefore termed 'complete outflow block' (COB).

Group 2 (COB/PCT). The above procedure was also carried out in five dogs but PCT, as described by Child *et al.*,[4] was performed at the same time (Fig. 1).

Group 3 (POB and PCT). The ameroid constrictor was omitted in five dogs so that the LHV was not constricted thus producing a 'partial outflow block' (POB). All five dogs were studied for several weeks and then PCT was performed as a second operation. At this time dissection of the portal vein was difficult and vessels entering this vein close to the liver were not divided as was the case in group 2.

Estimated Hepatic Blood Flow (EHBF)

EHBF was determined by measuring the plasma clearance and arterio-hepatic venous dye extraction ratio following a single injection (0.5 mg/kg) of indocyanine green (ICG).[2] EHBF was determined 2–3 days after operation and at intervals thereafter, and expressed as ml/min/kg initial body weight. Actual body weight at the time of estimation of blood flow could not be used because of the presence of ascites.

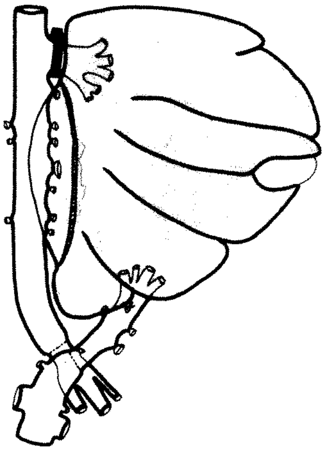

FIG. 1. Schematic representation of the combined procedure of complete outflow block and portacaval transposition (COB/PCT). Five lobes of the canine liver and the position of the gallbladder are shown. The right hepatic veins have been ligated and divided and the constrictor placed around the LHV. The two anastomoses between portal vein and IVC are indicated by dotted lines. The prolonged hepatic vein catheter is not illustrated.

Statistical Analyses

The results are expressed as mean ± standard deviation (SD) and analysed by Student's t test for paired or unpaired data as appropriate.

Results

Group 1 (COB)

Survival. In three of the 19 dogs in this group, PCT was also performed as a second operation but was unsuccessful for technical reasons and because of the poor condition of the dogs. Two other dogs were sacrificed, one died from an anaesthetic mishap and thirteen died from various causes 14–48 days (mean 29.8 ± 11.9 (SD)) after operation. In seven the cause of death could not be determined but ulceration of the stomach and/or duodenum was found in 15 of 16 dogs examined at necropsy. Four dogs died with perforated ulcers.

Ascites. Eighteen dogs had accumulated from 0.5 to 9.7 litres (mean 4.2 ± 2.4 (SD)) of ascitic fluid when measured at post mortem or operation.

EHBF. Two to three days after operation EHBF was 36.2 ± 9.3 (SD) ml/min/kg, a value which was not significantly different ($p > 0.1$) from that obtained in normal dogs in this laboratory[2] (31.3 ± 7.9 (SD) ml/min/kg). Subsequent estimations could not be made because of abnormal plasma clearance and extraction of ICG.

Group 2 (COB/PCT)

Survival. All five dogs died 32–88 days (mean 47.8 ± 23.8 (SD)) after the combined operation, a survival time that was significantly greater ($p < 0.05$) than for group 1. At necropsy gastroduodenal ulcerations were found in all five dogs but the exact cause of death was uncertain. Both anastomoses of the PCT were patent in all five cases.

Ascites. Four of the dogs accumulated 2.5 to 7.0 L (mean 4.1 ± 2.8 (SD)) of ascitic fluid by the time of death. In one of these the ascites disappeared after 21 days but reaccumulated 64 days after operation.

EHBF. EHBF was determined two to four times after the operation and in general values declined during the period of study (Fig. 2). Four dogs were studied on each of three occasions and mean flow significantly decreased ($p < 0.05$) from 38.4 ± 6.2 (SD) ml/min/kg to 17.7 ± 10.2 (SD) ml/min/kg after about four weeks. EHBF at three days was not significantly different ($p > 0.5$) from the equivalent values in group 1, but was significantly higher ($p < 0.05$) than normal for this laboratory.[2]

Immediately after operation, portal pressure was unchanged but there was a significant increase ($p < 0.01$)

in IVC pressure from a mean of 9.7 ± 1.4 (SD) to 14.4 ± 2.2 cm saline.

The longest surviving dog in this group was found to have complete reversal of portal flow into the IVC when contrast medium (HYPAQUE 45%) was injected into the portal vein 66 days after operation (Fig. 3).

Group 3 (POB + PCT)

Survival. PCT was performed 37–93 days after the POB procedure when all five dogs were in good condition. Two dogs died 46–84 days after PCT, one from a perforated duodenal ulcer and the other from pyonephrosis due to accidental ligation of the right ureter. Three dogs were sacrificed whilst still healthy, 63, 65 and 254 days after PCT. The performance of PCT was made difficult by the presence of adhesions, hepatomegaly and portal hypertension (in three dogs) following the first operation. Probably because of this, the distal IVC to proximal portal vein anastomosis was not performed well in the first dog studied and was found to be almost completely occluded at necropsy. Portal pressures in the three dogs with prolonged hepatic vein catheters[2] at the time of PCT were 15.5, 16.7 and 22.4 cm saline compared with the preoperative values of 10.2, 8.9 and 9.5 cm saline respectively. The catheter had been removed in the other two dogs prior to PCT and portal pressures were normal at the time of this second operation. Four dogs had gastroduodenal ulcers and in one of these the ulcer had perforated.

Ascites. None of the dogs developed ascites either before or after PCT.

EHBF. The values of EHBF before and after PCT are shown in Fig. 4, and despite some individual fluctuations remained relatively constant and normal. The mean flow calculated from 15 estimations in the five dogs before PCT was 31.4 ± 5.9 (SD) ml/min/kg and from 12 estimations after PCT was 31.4 ± 7.7 (SD) ml/min/kg, values that were not significantly different from each other nor from normal values.

That caval blood entered the liver via the anastomosis between IVC and portal vein was demonstrated by cineangiography in one dog 58 days after PCT (Fig. 5). Relatively normal filling of the left side of the portal tree contrasts with the reduced and stunted appearance of the venules supplying the right lobes.

Discussion

The early death of dogs with COB and the development of gastroduodenal ulcerations was unexpected in view of the reports by Orloff and coworkers[16,17,19] on the use of this model in long term studies. Generally there were no obvious causes of death, although the degree of liver damage was extensive when assessed histologically and biochemically (unpublished observations). Outflow block may have developed more rapidly in the dogs in the present study because of the use of the ameroid constrictor technique and the prolonged catheterisation of the left hepatic vein.

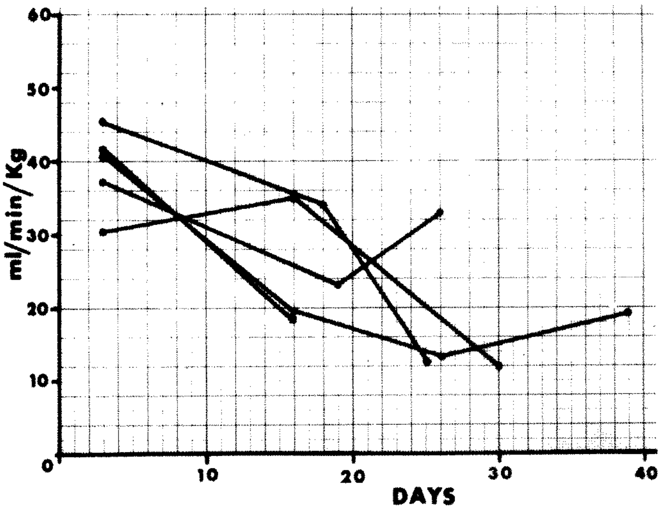

FIG. 2. EHBF in 5 dogs with COB/PCT (Group 2).

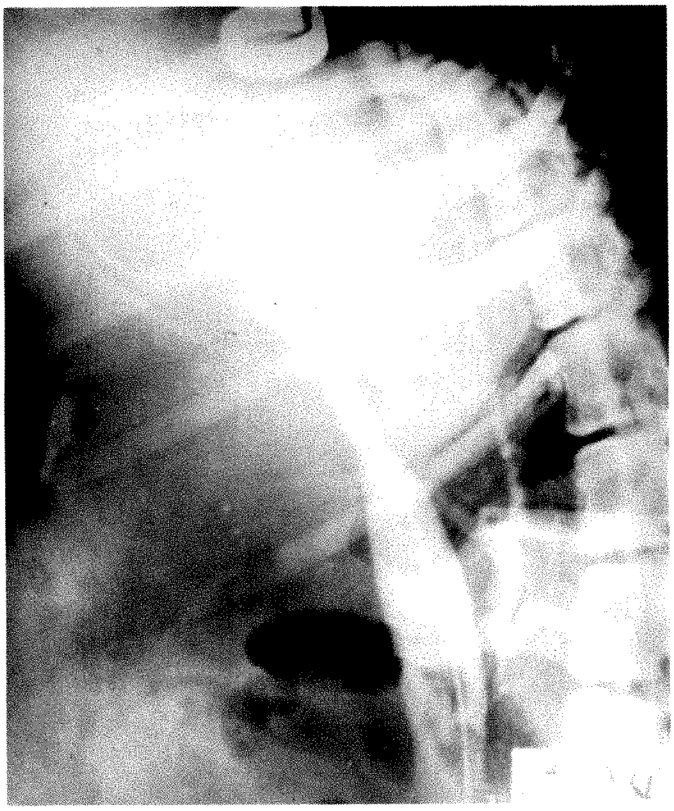

FIG. 3. Retrograde portal flow into the IVC in a dog with COB/PCT 66 days after operation. HYPAQUE (45%) was injected into the portal vein via a catheter placed through the anastomosis with the IVC after introduction via the femoral vein. Part of the paravertebral collateral system is also opacified and the stainless steel disc holding the ameroid constrictor around the LHV is seen at the top of the picture.

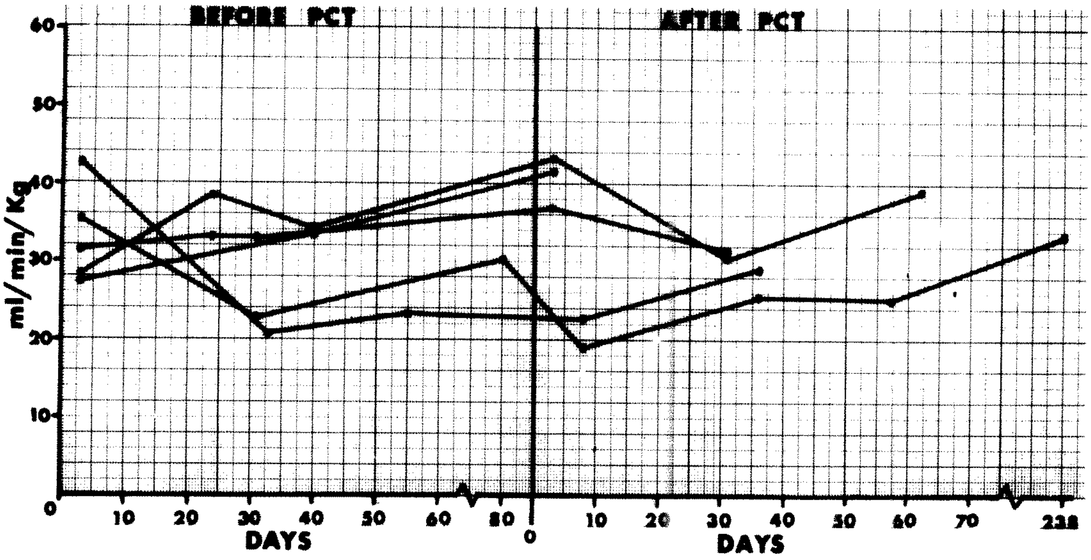

FIG. 4. EHBF in 5 dogs with POB before and after PCT (Group 3).

Because of the poor survival rates with COB alone, PCT and COB were performed at the same time in five dogs. This is, of course, not an ideal means of assessment, although such an approach has been used to study the effects of PCS on dogs with COB.[15] However, PCT did not maintain normal hepatic blood flow and it would appear that a venous inflow to the liver, whether portal or systemic, cannot be maintained in the presence of severe postsinusoidal obstruction as occurs in the COB preparation.

The findings in dogs with partial outflow block are similar to those obtained by Heer *et al.*[8] in dogs with carbon tetrachloride induced cirrhosis. That is, where the preoperative blood flow is not impaired, suggesting a moderate degree of liver disorder, PCT has little or no effect on EHBF. The normal hepatic blood flow obtained in dogs with POB was due to a continuing venous inflow into the portal bed. The latter is, however, only comparatively normal in those lobes having relatively undisturbed venous drainage. In contrast, when obstruction of the hepatic venous outflow tract involves all the lobes of the liver venous inflow in not maintained and indeed the portal vein may eventually act as an outflow tract. PCT also failed to prevent the accumulation of ascitic fluid in four of the dogs with COB further indicating continued imbalance of hepatic haemodynamics.

Recently Kreuzer and Schenk[9] reported increases in the venous supply to the liver four weeks after PCT had been performed in dogs with cirrhosis induced by dimethylnitrosamine. This agent produces an histological picture similar to Laennec's cirrhosis in man,[12] and the reduction in total hepatic blood flow prior to PCT observed by Kreuzer and Schenk[9] was due almost entirely to a decrease in portal flow. These conflicting results may be explained by the different models of experimental cirrhosis, although in addition Kreuzer and Schenk[9] measured hepatic blood flow with electromagnetic flowmeters as compared with the dye clearance technique used in the present study. The flowmeter method requires the placement of close fitting probes around the portal vein and hepatic artery at laporotomy and some interference with blood flow to the liver is always a possibility.[26] It remains to be shown whether normal blood flow is maintained for periods longer than 4 weeks in dogs with dimethylnitroasamine induced cirrhosis, and these results are eagerly awaited.

The failure to obtain reliable extraction ratios in the dogs with COB alone may indicate grossly abnormal intrahepatic haemodynamics since the same hepatic venous sampling technique was used in the COB/PCT group where the extraction pattern was normal. In this group adequate sampling of blood from the LHV was not obtained in the one dog studied 66 days after the operation and complete reversal of portal flow was demonstrated at this time. Presumably the blood leaving the liver was of arterial origin. The collateral system associated with the IVC is well developed in the dog,[14,15,20] as it is in man,[5] and appears to have the capacity to return to the heart not only venous blood from the lower regions but also hepatic arterial blood leaving the liver via the portal vein. In the event of PCT being performed in a patient whose hepatic lesion progressed this collateral system might be expected to prevent any haemostasis in the lower systemic venous system due to obstruction of caval flow throughout the liver. The efficiency of this collateral system was demonstrated in one case where PCT was performed in a child with glycogen storage disease.[27]

However, the results presented in this paper indicate that PCT would probably be of little benefit in cases of advanced cirrhosis since the potential advantage of this procedure, namely maintenance of venous inflow to the liver, is not apparently realised. Where the haemodynamic derangement of the liver is less severe PCT may be preferable to PCS in some selected cases.

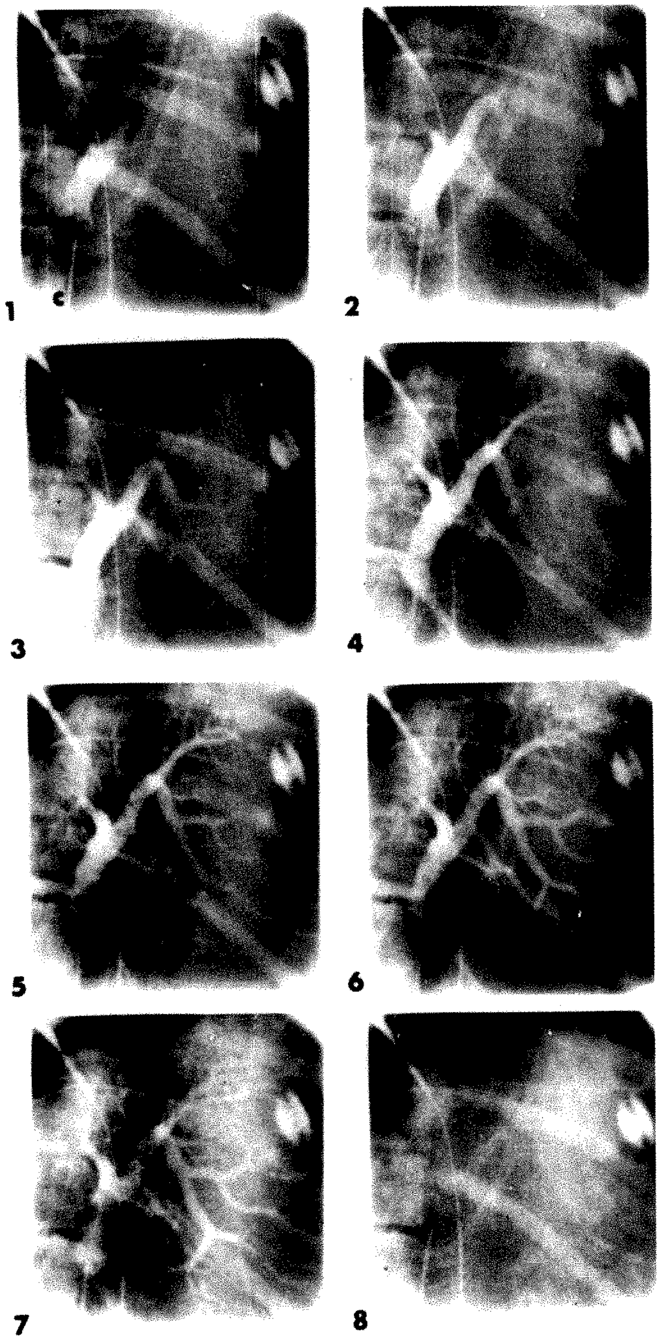

FIG. 5. Cineangiography in a dog with POB + PCT 58 days after PCT. The end of the catheter (c) was placed in the portal vein following introduction via the femoral vein and IVC. A bolus of HYPAQUE (45%) was injected during frames 1 to 3. The left side of the portal free (right side of Figure) appears to be relatively normal but the right side is reduced and stunted. h = prolonged hepatic vein catheter. b = nylon button anchoring the catheter as described by Baker and Shields.[2] Time intervals: Frames 1 to 7, 4 seconds; 7 to 8, 5 seconds.

Acknowledgments

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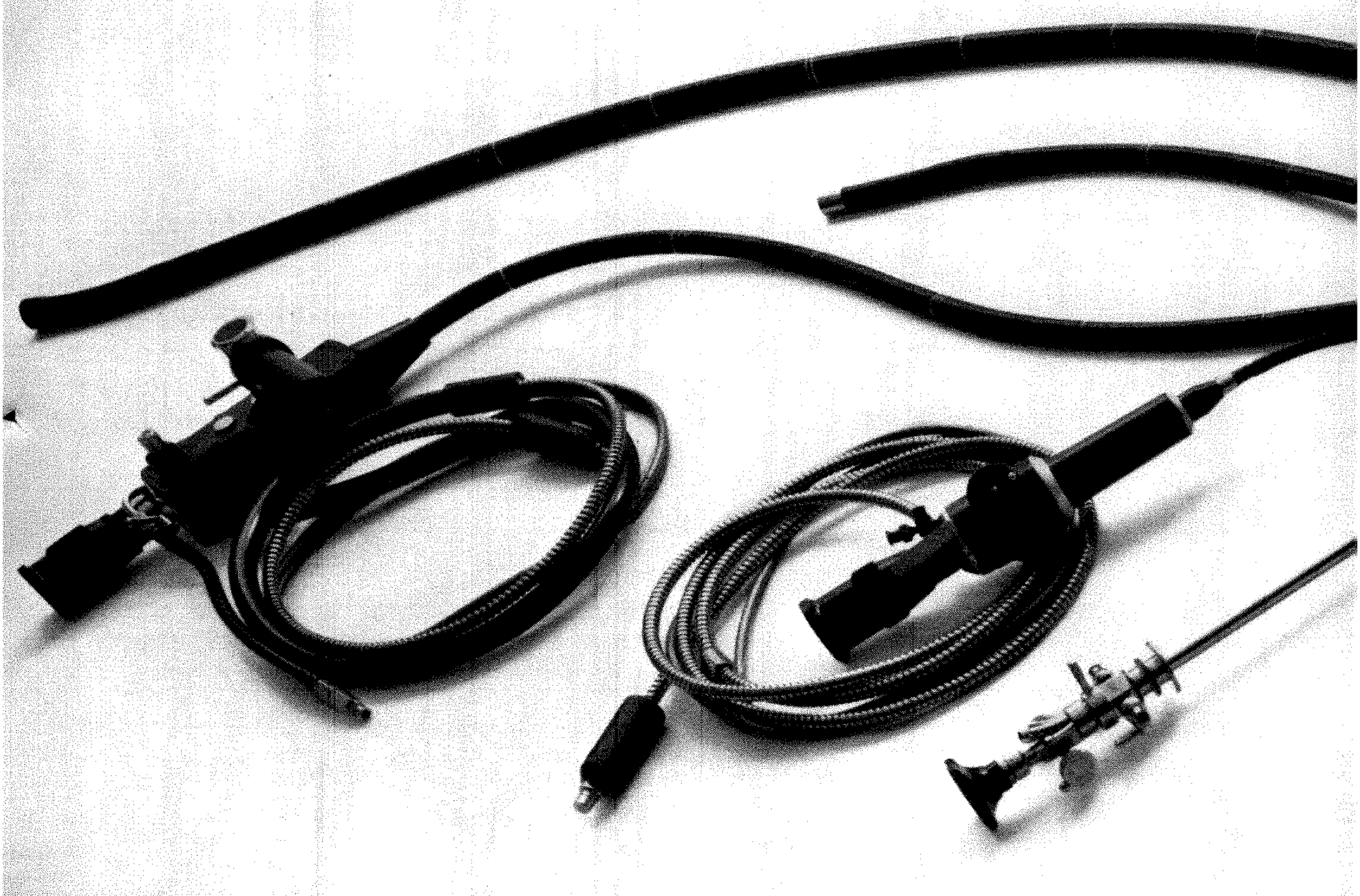

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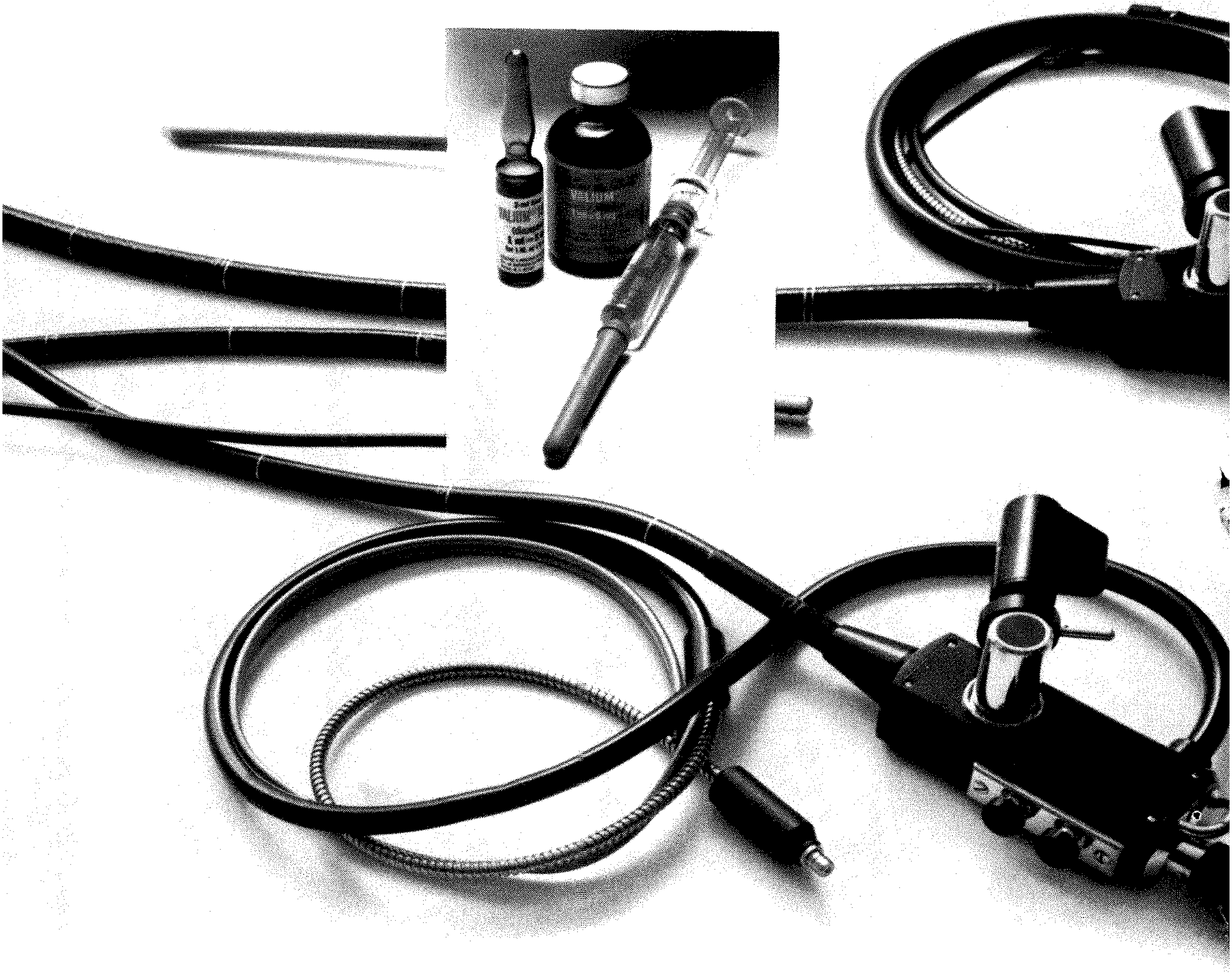

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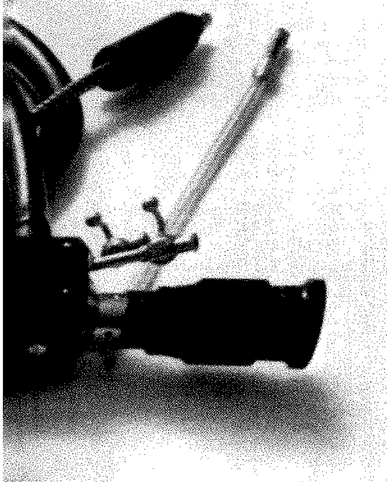

to reduce or eliminate need for narcotics,

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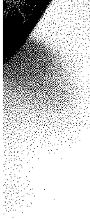

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How to administer Injectable Valium	Immediately prior to procedure, inject Valium slowly, taking at least one minute for each 5 mg (1 ml) given. Do not use small veins, *i.e.*, on the dorsum of the hand or wrist. Extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute Injectable Valium with other solutions or drugs; do not add to I.V. fluids.
How much to administer	Titrate I.V. dosage to desired sedative effect. Generally 10 mg or less is adequate, but up to 20 mg I.V. may be given, particularly when concomitant narcotics are omitted. If I.V. is not feasible, give 5 to 10 mg I.M. about 30 minutes prior to procedure.
Reduction of narcotics	Reduce narcotic dosage by at least a third. In some cases, narcotics may be entirely omitted.
Concomitant use of topical anesthetics	In peroral procedures, increased cough reflex and laryngospasm may occur; application of a topical anesthetic is therefore advisable. Necessary countermeasures should be at hand.
Patient response to look for	Calming effect usually becomes apparent within minutes. Generally, slurring of speech is indicative of sedative response desired. Drowsiness may occur, but patient usually is easily aroused to comply with instructions. Venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment have been reported.
About the elderly or debilitated	Lower doses—usually 2 to 5 mg—with slow increase are recommended.
Resuscitative equipment	Because of the possibility of apnea and/or cardiac arrest, particularly in the elderly and very ill patient and those with limited pulmonary reserve, resuscitative facilities should be immediately available.
What to tell the patient to expect	Explain that he will feel less anxious; that he may be drowsy but he will hear what is said; that there may be a bit of discomfort when instrument is inserted but that his cooperation will be helpful to himself and everyone concerned.

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Contraindicated: In infants; in patients with known hypersensitivity to the drug; in acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *When used I.V., the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment. Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Administer with extreme care to elderly or very ill and those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; have resuscitative facilities available. When used with narcotic analgesic eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, nursing women or women of childbearing potential, weigh expected benefit against possible hazard to mother and child. Not recommended for OB use.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm and increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic and have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly and debilitated; safety and efficacy in children under 12 not established.

Adverse Reactions: Drowsiness, fatigue, ataxia, fusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 min. prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma and diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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Burn Scar Carcinoma and Hypercalcemia

ROBERT E. GERNER, M.D.,* GEORGE E. MOORE, M.D., Ph.D.†

A case of a patient with burn scar carcinoma of an extremity associated with hypercalcemia and without bone metastasis is presented. From the data presented, it seems reasonable to assume that this squamous cell carcinoma of a burn scar secreted some type of parathyroid hormone-like substance or substances which posessed calcium-increasing biological activity resulting in hypercalcemia.

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SQUAMOUS CELL CARCINOMA is known to occur in old burn scars, however, the true incidence of this relatively rare occurrence following severe burns is unknown. The syndrome of hypercalcemia associated with nonparathyroid neoplasms without bone disease is also relatively rare.

In 1969, Omenn[8] collected and reviewed 73 cases on pseudohyperparathyroid syndrome and in this group, more than half were renal cell carcinoma and squamous cell carcinoma of the lung. Since then, a number of other cases have been reported and more recently, this syndrome has been reported in breast carcinoma[6,7] and familial pheochromocytoma.[13]

This report concerns, to our knowledge, the first reported case of a squamous cell carcinoma occurring in an old burn scar associated with hypercalcemia and without evident bone metastasis. The serum calcium level returned to normal within 24 hours after removal of the primary lesion of the extremity.

Case Report

C.B., a 38-year-old white male, sustained second and third degree burns of both upper extremities at the age of three, which were not grafted and healed by scarring. In 1969, at the age of 35, an area of the scar in the right upper arm was traumatized resulting in an abrasion which failed to heal. Squamous cell carcinoma of this chronic ulcerated area was confirmed by biopsy in July of 1970. This neoplasm was treated by wide excision and skin graft. Subsequently, during the following year several local recurrences in the right axilla were treated by excision and skin graft.

In March of 1972, when first seen by us, he had a draining sinus tract in the right axilla associated with a large recurrent 8 × 9 cm mass high in the axilla. There were severe burn scars of both upper arms extending into both axilla. His medical history was otherwise completely negative and, in brief, was a healthy, muscular individual with no other physical findings.

All hematological and biochemical studies were normal with the exception of a serum calcium of 13.5, 14.3 and 14.1 mg % performed on three separate preoperative days. In addition, the serum phosphorous levels were 2.8, 2.7 and 2.8 mg %. A chest x-ray including tomograms of both lung fields was negative for primary or metastatic disease. A skeletal survey including hands, feet and mandibles was negative.

The tumor mass was fixed to both the clavipectoral fascia and the fascia over the subscapularis and latissimus dorsi, but not firmly attached to the chest wall. It was concluded that a forequarter amputation was required for a total resection of the tumor mass.

On 3–28–72, a right forequarter amputation was performed. The pathology report described an 8 × 7 × 4 cm necrotic tumor mass of the axilla with invasion into the muscles and subcutaneous tissue. There was no bone involvement by the neoplasm. Eleven of 24 axillary lymph nodes contained metastatic tumor. Unfortunately, no tumor tissue was preserved for radioimmunoassay studies to determine the presence or absence of a parathyroid-like hormone (PTH).

On the first postoperative day, the serum calcium and phosphorous levels were 9.5 and 3.2 mg % respectively. These values, including the pre-operative and post-operative followup levels and total serum protein are shown in Fig. 1.

This patient has been followed at specified intervals for over 16 months without evidence of local or distant recurrence of tumor.

Radioimmunoassay studies of this patient's pre and postoperative sera for PTH were performed by Upjohn Laboratory Procedures.[4] These values are shown in Table 1.

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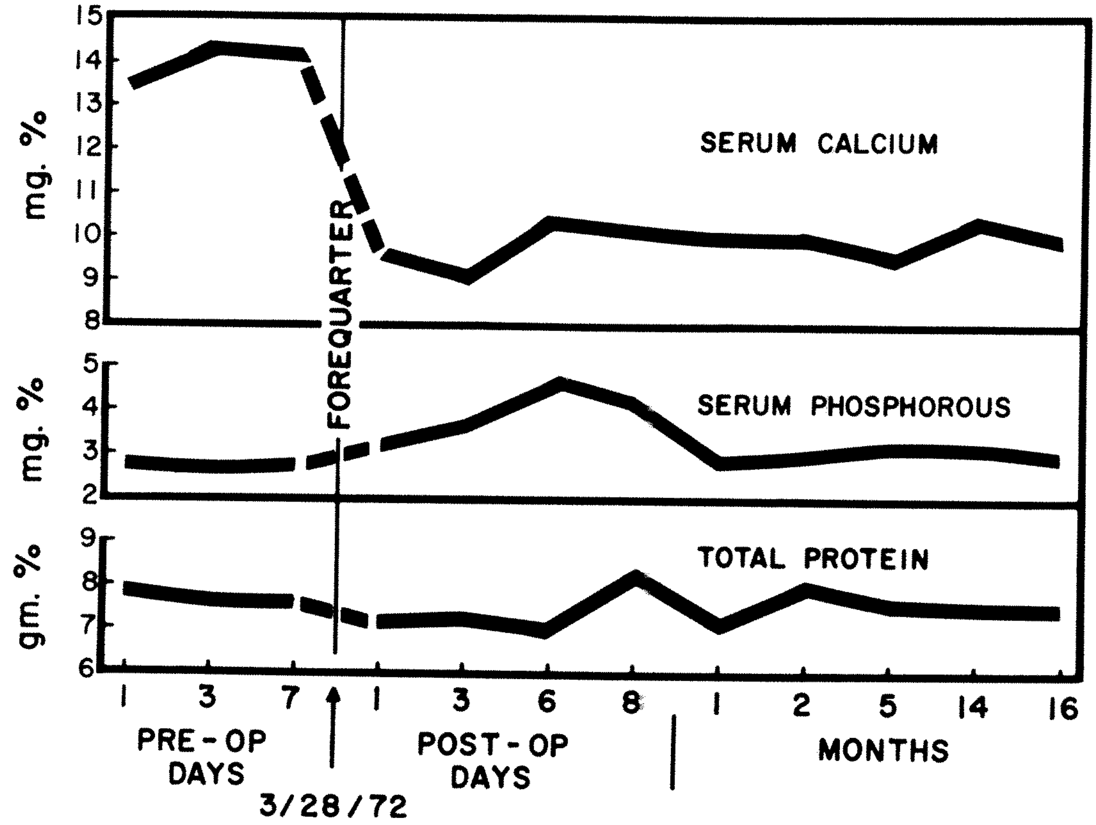

Fig. 1. Serum calcium, phosphorous and total protein.

Discussion

In the differential diagnosis of hypercalcemia, some of the causes to be considered include immobilization, metastatic bone disease, primary and tertiary hyperparathyroidism, blood dyscrasias, Paget's disease, hypervitaminosis D, milk-alkali syndrome, thiazide therapy, hyperthyroidism, and non-parathyroid tumors without bone disease that secrete PTH. A majority of the later are squamous cell carcinomas of the lung and renal cell carcinoma of kidney.

The immunoassay for parathyroid hormone (iPTH) in this patient's pre and postoperative sera gave values of 260 and 153 pg/mg respectively. The preoperative iPTH value could be listed as a high normal value, but yet within the normal range for that laboratory. In addition, at the present time, the immunoheterogenicity of circulating PTH, makes it impossible to measure absolute concentrations of the hormone in the plasma.[2] Following surgical removal of the tumor, there was an immediate return of the serum calcium to normal levels and a considerable decrease in the iPTH value. The postoperative followup of this patient has been over 16 months and during this interval, several serum calcium determinations have been within normal limits.

Table 1. *Results of Radioimmunoassay Studies*

	Serum Calcium	Parathyroid Hormone
Pre-op 3-24-72	14.1 mg %	260 pg/ml
Post-op 5-1-72	9.3 mg %	153 pg/ml
Normal	(9.0-10.5 mg%)	(255 pg/ml ± 46 pg/ml)

The immediate and substained reversal of this patient's hypercalcemia following wide excision of the burn scar cancer gives strong support to the contention that this squamous cell carcinoma produced PTH.

Albright[1] and others[5,9] postulated that non-parathyroid tumors associated with hypercalcemia, secreted a substance with an action biologically similar to that of parathyroid hormone. Subsequently, radioimmunoassays of sera and tumor tissue in a number of these cases, demonstrated a polypeptide which shared antigenic and physiochemical properties with parathyroid hormone.[3,4,10,11,14] In a search of the literature, we found no published reports of the successful extraction and biological assay of this material which would give good evidence that these tumors do indeed secrete biologically active parathyroid hormone.

As it becomes possible to assay various hormones, many additional kinds of tumors may be found to have an abnormal capacity to produce hormone-like substances that are inconsistent with the normal mature cells of the tissue of origin. Cell culture methods may be very helpful in future studies of these interesting expressions of cellular phylogenesis.

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Reversal of Capillary Stasis and Prevention of Necrosis in Burns

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It has been suggested that the ultimate depth of burn necrosis might be minimized by prevention or reversal of the progressive capillary stasis which occurs in the early postburn hours. To study the role of wound dehydration in determining burn depth, 5% body surface area, 75 C, 10-second burns (in which the zone of stasis included the full thickness of skin) were inflicted on the backs of guinea pigs and subsequent mechanical trauma was prevented. At various times postburn, water content, (and after India ink perfusion) depth of capillary stasis and histological structure of burn were studied in the following groups: 1) blister intact; 2) blister removed; and 3) blister replaced by several different types of dressing. Reversal of capillary stasis was least and necrosis full-thickness in depth in undressed wounds with blister removed. Reversal of capillary stasis was complete and necrosis absent with blister replaced by fresh split-thickness porcine skin and correlated with prevention of wound dehydration. Similar, though less complete, prevention of necrosis occurred with blister intact or replaced by sialastic film. Other dressings were associated with deep necrosis or gross infection. These and other data suggest that in the zone of stasis, capillary stasis may be reversed and necrosis avoided by appropriate prevention of wound dehydration. Clinical correlations are suggested.

EVEN BRIEF CONTACT with high temperature heat sources such as flame or molten metal commonly produces immediate coagulation of a variable depth of skin.[11] In addition, just below the tissue undergoing immediate coagulation necrosis is a "zone of stasis" where progressive microvascular stagnation leads to deepening capillary occlusion (stasis) during the first day or so postburn.[6,15] Believing that prevention or reversal of capillary stasis might diminish the ultimate depth of burn necrosis, some authors have advocated the use of anticoagulants[13,14] or desludging agents.[1] Others have suggested that tissue death in the zone of stasis is not due to stasis per se but to the direct effects of heat,[7,17] implying that such efforts would be futile.

This experimental study presents evidence that the primary cause of necrosis in the zone of stasis is neither heat nor vascular occlusion, but wound dehydration. The study further demonstrates that in this zone, capillary stasis may be reversed and necrosis prevented by appropriate prevention of wound dehydration.

Materials and Methods

Standard Burn Preparation

In groups of 12, white male guinea pigs weighing 337 ± 46 gm (mean ± 2 standard deviations) were anesthetized by intraperitoneal injection of sodium pentobarbitol (35 mg per kilo). Guinea pigs were used because among common small laboratory animals, their skin exhibits the least variability in thickness.[19] To avoid epithelial trauma due to shaving, dorsal trunk hair was clipped and the remaining stubble washed off in tap water after application of a calcium thioglycolate containing depilatory. A 5% body surface area, 75 C, 10-second scald burn was then inflicted on the depilated area using a specially designed restraining apparatus.[18]

Although in guinea pigs, heat-injured epidermis is not spontaneously separated by blister fluid at the dermal-epidermal junction, its adherence is greatly weakened[16] and it is easily separated at this junction by gentle shear-

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ing pressure. In preliminary studies it was found that the burned animal itself frequently caused disruption of this "blister" and injury to deeper portions of the burn. In this study, such trauma was prevented by placing each animal in a separate cage immediately postburn after it had been fitted with an elastoplast trunk binder having a padded aperture surrounding and protecting the burn.

Determination of Water Content, Depth of Capillary Stasis, and State of Healing

At specified times postburn, each animal was reanesthetized and a centrally located 1 cm^2 specimen of burned skin including the panniculus carnosus biopsied and immediately weighed. The percentage of burn water content was determined from the weight loss measured after drying the specimen to constant weight at 50 C for 48 hours. After biopsy, each animal underwent cannulation of the ascending aorta and perfusion with 60 cc of India ink at 400 mm Hg. By trial and error, this combination of perfusion volume and pressure was found necessary to insure complete filling of all patent skin capillaries. Burn specimens adjacent to the biopsy site were then removed for histological examination of the state of healing and depth of capillary stasis (as indicated by the absence of intracapillary India ink).

Survey of the Effect of Various Dressings

In this country, local wound care most commonly includes early removal of burn blisters. Therefore, on the seventh postburn day (PBD), water content, depth of capillary stasis, and state of healing of burn were studied in groups of animals treated during the postburn period in one of the following ways: 1) blister intact; 2) blister removed immediately postburn by gentle digital shearing pressure; 3) blister removed immediately postburn and replaced by a light gauze dressing holding in contact with the wound a sterile sheet of saran; 4) polyethylene film; 5) vaseline impregnated fine mesh gauze; 6) sialastic film bonded to a single layer of fine mesh gauze in contact with the burn;* or 7) fresh split-thickness porcine skin.†

Detailed Comparison of Exposure vs. Split-thickness Porcine Skin Dressings

At various times postburn (4 minutes, 2, 4, 8, and 16 hours, and 1, 2, 4, 7, and 14 days postburn), water content, depth of capillary stasis, and state of healing of burn were determined in groups of 12 animals treated during the postburn period with blister removed immediately postburn, and subsequently 6 treated open and 6 treated with porcine skin.

Effects of early removal of porcine skin dressings were studied by determination of depth of stasis and state of healing on the seventh PBD in groups of animals having the burn blister replaced by porcine skin dressings immediately postburn and subsequently removed at 2, 4, and 6 days postburn.

Results

The Standard Burn

The time and temperature combination chosen for the standard burn (10 seconds and 75 C) produced no coagulation of skin immediately postburn: grossly the burn blanched on pressure and histologically, circulation remained intact in the most superficial capillaries. In fact, except for separation of squamous epithelium, occasional slight disruption of the dermal-epidermal junction, and reduction of basophilia in epithelial cells, burned skin was not histologically distinguishable from normal skin immediately postburn (Fig. 1).

During the early postburn hours, however, capillary flow ceased in progressively deeper layers of skin until by 16 hours postburn, capillary stasis extended well beyond the deepest hair follicles and almost to the panniculus carnosus. The zone of capillary stasis in the burn preparation used in this study, therefore, included the full thickness of skin, although patent arterioles remained visible here and there within the zone of capillary stasis as illustrated in Fig. 2, 16 hours postburn.

Effect of Various Dressings

In surveying burns treated for one week with blister intact, blister removed, or blister replaced by several different types of dressing, it was found that depth of necrosis was greatest (full-thickness without surviving hair follicles) and healing least (incomplete or absent epithelialization from the wound edges) in undressed wounds with blister removed. Conversely, at 1 week postburn, there was no evident necrosis and complete epithelialization from surviving hair follicles in wounds with blister replaced by split-thickness porcine skin. Similar, though less complete, reepithelialization from surviving hair follicles and prevention of necrosis occurred with blister intact or replaced by sialastic film. Other dressings were associated with full-thickness or deep partial-thickness necrosis (vaseline dressings), or gross purulence (saran, polyethylene film).

Comparison of Exposure vs. Porcine Skin Dressing

As maximum conservation of tissue in burns with blister removed appeared to occur in those treated with porcine skin, and the deepest necrosis appeared to occur in those left exposed, a more detailed comparison of the two

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* Provided by Edwards Laboratories, Santa Ana, California.

† Provided by Burn Treatment Skin Bank, Phoenix, Arizona.

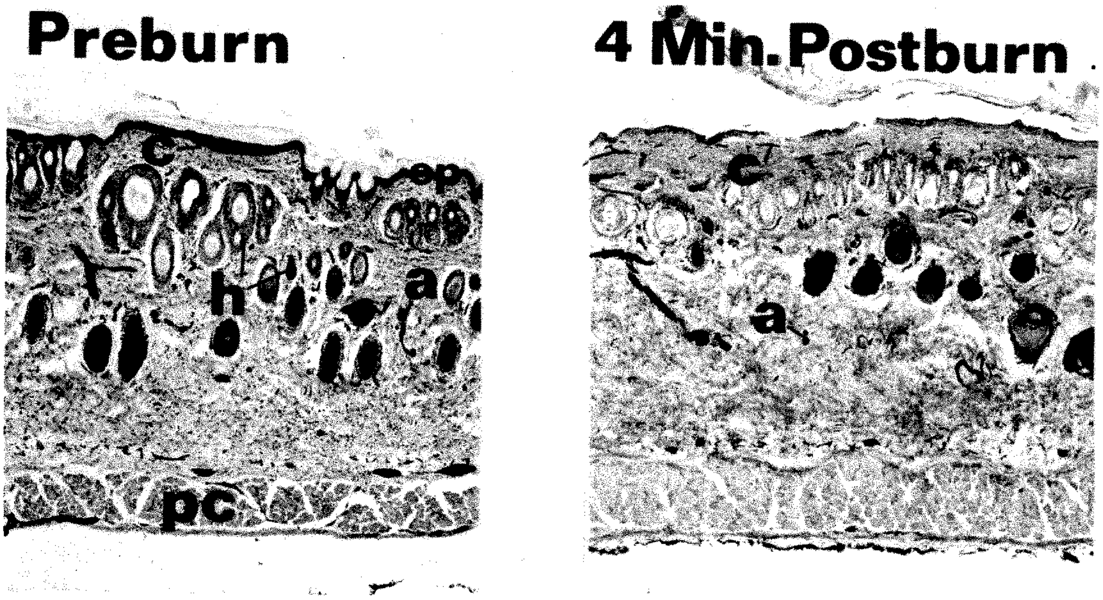

FIG. 1. Guinea pig skin before and 4 minutes after burning showing, by the presence of India ink perfusate, persistent circulation in superficial capillaries. ep = surface epithelium; pc = panniculus carnosus; h = hair follicles; a = patent arteriole; c = most superficial patent capillary (H & E × 40).

groups was carried out at frequent intervals postburn and is illustrated in Fig. 2.

In both groups by 16 hours postburn (and with little change at 24 hours postburn) capillary stasis progressed to full thickness in depth, i.e., below the base of hair follicles and almost to the panniculus carnosus. After the first PBD, however, a striking difference became evident in the capillary circulation of exposed and porcine skin treated burns: In porcine skin treated burns, by the second PBD, circulation was restored in previously occluded capillaries surrounding the deepest hair follicles. By the fourth PBD, in this group, capillary circulation was intact almost to the dermal surface and it was fully restored by the seventh PBD. In exposed burns, however, while some reversal of capillary stasis did occur, it never extended more superficially than it had by the second PBD, and never to the deepest hair follicles, let alone to the original dermal surface. The extravasation of perfusate evident in Fig. 2 at 2 days postburn was a consistent finding in both groups and suggests a temporary lapse of tolerance to

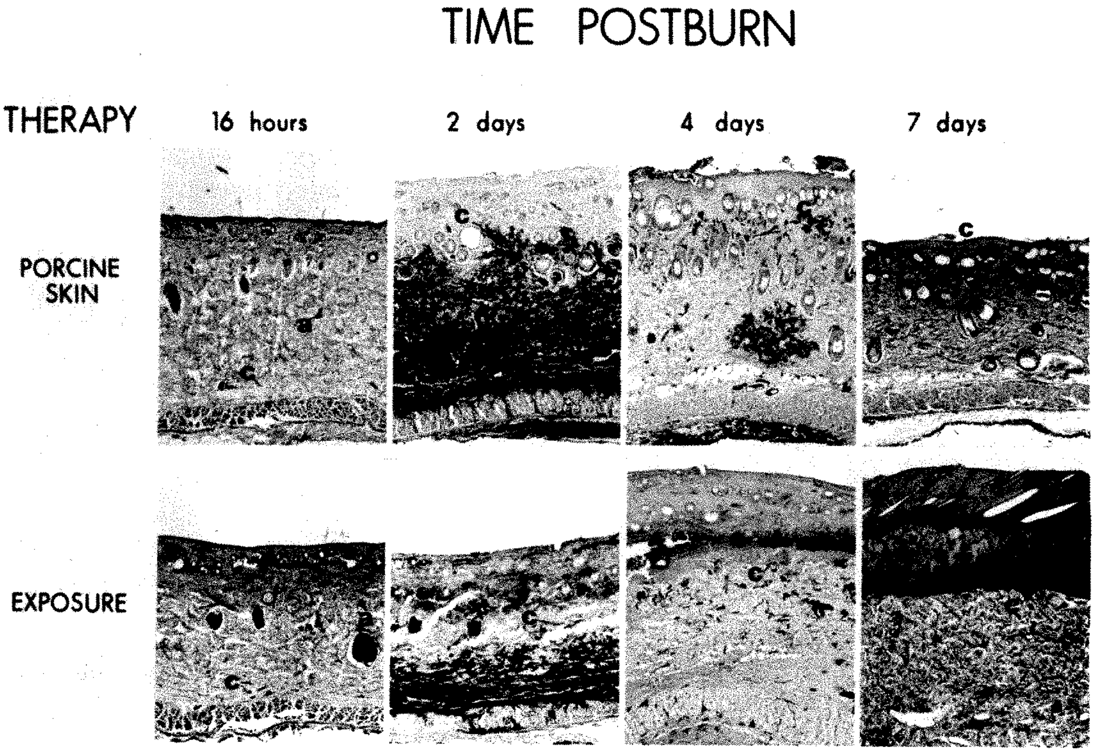

FIG. 2. Guinea pig skin following India ink perfusion at various times after burning and blister removal showing reversal of capillary stasis and prevention of necrosis by application of porcine skin. Abbr. as in Fig. 1 (H & E × 17).

intraluminal pressure when occluded vessels first reopen.

Figure 2 also illustrates that burns in the porcine skin treated group exhibited no signs of dehydration, and reepithelialization was complete by the seventh PBD. Furthermore, nuclei and basophilia which faded histologically from hair follicle epithelium with the cessation of capillary flow, reappeared as capillary stasis was reversed in this group. In contrast, by 16 hours postburn, and in some specimens by 8 hours postburn, the histological changes associated with dehydration were obvious in the upper one-quarter of exposed skin, and progressed to include the base of hair follicles by 2 days postburn. By the fourth PBD, and even more obviously by the seventh, the strata of burn dehydrated by exposure became obviously necrotic and began to separate from the underlying tissue which showed no evidence of surviving hair follicles. Figure 3 illustrates that in correlation with these histological findings, the water content of exposed burns was significantly lower than that of porcine skin treated burns by 16 hours postburn, and remained so until after the first week postburn.

In summary, therefore, subsequent to full-thickness dehydration, revascularization of hair follicles did not occur in exposed burns and the full thickness of skin became necrotic. By comparison, porcine skin treated burns in which no dehydration occurred showed no necrosis, full reversal of capillary stasis, return of hair follicle epithelium to histologic normalcy, and full epithelial resurfacing by the seventh PBD.

When porcine skin applied to deblistered burn immediately postburn was removed 2, 4, and 6 days postburn, at 1 week postburn depth of necrosis was less and revascularization was more complete the later porcine skin dressings were removed. However, the complete healing and absent necrosis seen in burns with uninterrupted coverage by porcine skin was never achieved.

Discussion

From his careful work on guinea pig burns in 1949, Sevitt[15] concluded that capillary stasis in burns was "irreversible," and that "the most deeply situated hair follicles become necrotic (if not already so from direct heat effects) when stasis involves the capillaries in the deepest part of the dermis and full-thickness loss of the skin follows."[17] In 1953, Jackson's[6] now classic observations of human burns with blister removed led him to confirm Sevitt's conclusions: as he summarized it in a later review, "Treated by creams or by exposure, the zone of stasis and the coagulated zone inevitably separate as slough."[7]

In 1969, however, Jackson himself began to have "second thoughts" about the nonviable state of the zone of stasis.[7] He observed the following paradox when tangential excision of a recent burn revealed a dermal surface within the zone of stasis: the same dermal surface which looked "dead" histologically and became a dry brown slough if ungrafted and dressed with vaseline gauze ("It must be dead"), also bled from a few scattered arterioles and accepted autograft ("It must be alive").

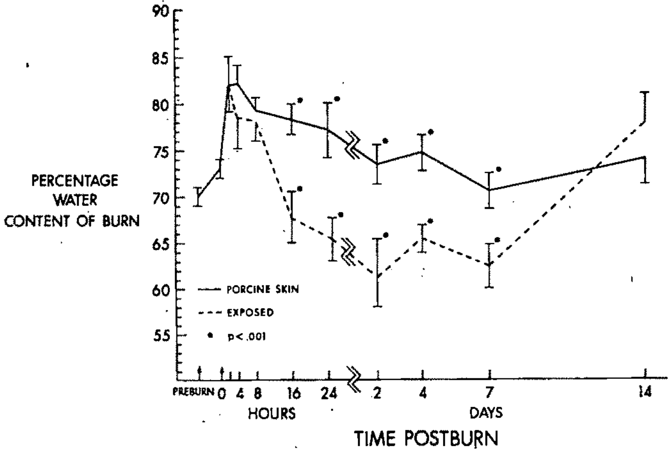

Fig. 3. Water content of deblistered guinea pig burns during 2 weeks of exposure or coverage with porcine skin. Mean and 95% confidence limits are indicated for each value except where clarity required omission of overlapping confidence limit brackets.

The present study appears to explain Jackson's paradoxical observations by contradicting Sevitt's conclusions.

In the preliminary phases of the present study, we, like Sevitt, found that our standard 75 C, 10-second guinea pig scald burn frequently produced full-thickness skin loss as well as full-thickness capillary stasis. It was then noticed, quite by chance, that full-thickness skin loss occurred *only* in those animals who had removed the blister from their burns, presumably by scratching or rubbing against the cage walls, etc. As Billingham pointed out, guinea pigs are notorious traumatizers of experimental wounds.[2] Because the burns on Sevitt's animals were both unprotected and, apparently ventral or ventrolateral in position, mechanical blister disruption would have been very likely. Such trauma may explain the full-thickness loss Sevitt found in burns exhibiting capillary stasis. Clearly it did for us, because with mechanical trauma eliminated and dehydration prevented by application of porcine skin to the deblistered burn, we found that full-thickness "irreversible" capillary stasis was completely reversed and necrosis avoided. Because almost as complete a reversal of stasis occurred with the original blister intact or replaced by a sialastic film, simple maintenance of wound hydration seems the most probable explanation for this phenomenon rather than some occult or peculiar property of living or biological membranes.

Let us reconsider Jackson's paradoxical observations in the light of our data. Like Jackson who removed water-retaining epidermis by tangential excision or by removal of the burn blister, we found that with epidermis removed the zone of stasis dehydrated and sloughed even when covered by supposedly occlusive (vaseline) dressings. When Jackson prevented dehydration by application of fresh human skin graft to the excised or deblistered surface of the zone of stasis, circulation eventually returned to the surface as in our porcine skin treated burns and revascularized the graft. It is a tribute to Jackson that these manifestations of reversible capillary stasis were noted so accurately before the data of the present study were available. Had he not pointed it out, we might not have recognized the occasional patent arteriole and the histologic fading of nuclei and basophilia from epithelial cells in the zone of capillary stasis. It is tempting to speculate that the striking return of epithelial cells to histologic normalcy as stasis is reversed reflects the return of normal nuclear and cytoplasmic functions e.g., cell division and respiration.

Prevention of dehydration probably explains the now very frequent observation that superficial partial-thickness (second degree) burns heal more rapidly, with less scar and better pigmentation, etc. when blister is left intact[4] or replaced by homograft,[9] heterograft,[3,8] or even transparent adhesive tape.[10] As dehydration of exposed deblistered burns is evident as early as 8 to 16 hours postburn (and may be present though not evident earlier) and can also occur if porcine skin is removed too early, an early start and proper duration of treatment may be important to success. Occasional dissenting reports[5] concerning the value of porcine skin in treating second degree burns may be attributable to such factors.

It is instructive to consider in retrospect how the testimony of skilled observers suggested but did not previously lead to the conclusions of this study. The contributions of Sevitt and Jackson have been discussed. Miller[10] noted that after 72 hours of pallor (capillary stasis) under transparent adhesive tape or homograft, deblistered second degree burn in man became pink and could vascularize split-thickness homograft i.e., capillary circulation was reestablished. Order et al[12] briefly noted the reopening "by an inapparent mechanism" of previously occluded suprapannicular arterial circulation during the first and second postburn day in "second degree" rat burns, but did not extend this observation to the phenomenon of capillary stasis.

Perhaps most sobering has been our disregard for the testimony of historically our most valued observer, the patient himself. When in shock he asks for "Something . . . anything to drink!"; when burned he asks for "Something . . . anything to cover the burn!" When virtually every standard manual of emergency burn care advises: 1) "*Primo non nocere*"; and 2) "Remove the blisters from second degree burn," perhaps we should pause and listen to the patient telling us "It was better with the blister on," especially when some of those manuals go on to advise actively drying the wound with heat lamps, currents of warm air, etc. As available evidence appears to confirm the intuition of our patients, if for various reasons we still believe blisters are best removed from second degree burns, we must seriously consider subsequent application of porcine skin dressing, or some equivalent technique, to avoid wound dehydration.

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Acute Hemodilution:

Its Effect on Hemodynamics and Oxygen Transport in Anesthetized Man

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The effects of acute normovolemic hemodilution on hemodynamics, oxygen transport, tissue perfusion and blood volume were studied. The subjects were four patients undergoing total hip replacement with prebleeding and hemodilution under fluoroxene and nitrous oxide anesthesia. The hematocrit was reduced to 29% and 21% by bleeding in two steps with simultaneous infusion of plasmanate and lactated Ringer's solution. The major compensation was a rise in CO to 123% and 136%. Systemic oxygen transport (COX arterial O_2 content) was only slightly reduced and the arteriovenous oxygen difference decreased. Tissue perfusion remained excellent. Blood volume was slightly expanded. The procedure was well tolerated by this group of selected patients, and homologous blood utilization was markedly reduced.

INTRAOPERATIVE HOMODILUTION has been practiced both in cardiac[14,16,25] and general surgery.[29] Advantages include avoidance of homologous blood transfusion with its attendant hazards including serum hepatitis, and conservation of blood. At the Peter Bent Brigham Hospital, prebleeding with hemodilution is used for patients undergoing major operations and cardiopulmonary bypass. Although the effects of chronic anemia have been well studied there are no detailed hemodynamic studies on acute normovolemic hemodilution in man. Safe limits of blood replacement with erythrocyte free solutions have not been well defined. Studies of the effects of acute normovolemic hemodilution in experimental animals[8,19,23] have shown an increase in cardiac output, with no increase in oxygen extraction ratio. In a study of normal volunteers in whom anemia was induced by gradual hemorrhage, there was no increase in cardiac output and a compensatory rise in oxygen extraction ratio was found.[34] The present study was undertaken to discover the effects of acute normovolemic hemodilution on hemodynamics and oxygen transport in anesthesized man, undergoing elective operation.

Methods

Four patients aged from 29 to 56 years undergoing total hip replacements with hemodilution were studied. Patients with cardiovascular, pulmonary and renal disease were excluded. The study was approved by the human studies committee of the hospital. After thorough explanation, informed consent was obtained from each patient.

On the day prior to operation, blood volume (BV) was measured with ^{51}Cr tagged autologous red cells for red cell mass (RV) and the Evans' blue dye method to measure plasma volume (PV).[3,22] The patients were anesthetized with thiopental (Pentothal) for induction and fluoroxene and nitrous oxide for maintenance. The patients were intubated and spontaneous respiration was permitted with 5% fluoroxene, nitrous oxide, and oxygen. Measured FiO_2 was in the range of 50%. Arterial $PaCO_2$ was kept constant (Table 1).

Blood vessel cannulations were done after induction: a radial artery line percutaneously; a four channel ther-

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TABLE 1. *Effects of Hemodilution on Oxygen Transport*

Measurements		Baseline	Hemodilution I	Hemodilution II	End Operation
Systemic O_2 Transport ml/min	ML	462	466	446	484
	SM	992	859	794	709
	RH	659	559	495	589
	SP	913	740	733	529
Mean	±SEM	756 121	656 88	617 85	578 48
Arterial O_2 Sat. Vol. %	ML	98.4	98.6	98.6	96.4
	SM	95.8	98.4	98.6	98.3
	RH	97.7	98.3	97.7	98.8
	SP	99.1	98.1	97.1	97.3
Mean	±SEM	97.8 0.7	98.4 0.1	98 0.4	97.7 0.5
Venous O_2 Sat. Vol. %	ML	96.8	96.9	96.3	78.6
	SM	91.0	91.5	89.9	61.2
	RH	73.3	70.1	64.0	58.9
	SP	93.7	91.1	92.4	87.3
Mean	±SEM	88.7 5.3	87.4 5.9	85.7 7.3	71.5 5.9
Arterial pO_2 mmHg	ML	198	218	213	114
	SM	250	263	278	117
	RH	238	234	251	209
	SP	322	332	333	298
Mean	±SEM	250 26	262 25	269 25	185 44
Venous pO_2 mmHg	ML	80	84.9	73	43
	SM	64	69.2	64.8	38
	RH	42	36.8	33.8	33.5
	SP	75.3	68.8	72.8	60.3
Mean	±SEM	65 9	65.0 10	61 9	44 6
A-V O_2 Content Difference Vol. %	ML	0.63	0.62	0.66	2.8
	SM	1.53	1.57	1.56	3.8
	RH	5.56	4.30	4.12	5.2
	SP	1.67	1.65	1.25	1.72
Mean	±SEM	2.35 1.1	2.04 0.79	1.89 0.76	3.38 0.74
Arterial pCO_2 mmHg	ML	40	38	38.3	36.6
	SM	43	43	43.7	39.7
	RH	37	31.1	27.7	35.6
	SP	45.8	42.7	42.1	44.8
Mean	±SEM	40.9 2.3	38.7 2.8	38.0 3.6	39.2 2.1

modilution Swann Ganz catheter was directed into the pulmonary artery via an antecubital venous cutdown so that one channel could be used to measure wedge pressures; two 14 gauge venous cannulae were placed percutaneously. An Instrumentation Laboratory (IL) right angle muscle surface pH electrode was inserted via a cutdown on the biceps muscle and pH measured using a Corning pH meter. Esoghageal temperature was monitored.

After a period of stabilization under anesthesia, baseline measurements were made. This was followed by two bleeds, designated Hemodilutions I and II. After each bleed there was a five minute stabilization period followed by measurement. Measurements were repeated at the midpoint and at the end of operation.

Hemodilutions I and II were conducted as follows. The patients were bled from venous and the arterial cannulae approximately 25% of their blood volume over a period of 20 minutes. Simultaneously a volume of Plasmanate* equal to that of the shed blood and an equal volume of lactated Ringer's solution was infused. Mean hematocrit after Hemodilution I was 29.3%, after Hemodilution II 21.5%. During operation blood loss was replaced with Plasmanate and lactated Ringer's solution, then by reinfusing the patient's own blood toward the end of the procedure.

Large vessel hematocrit (LVH) was measured in triplicate by centrifuging a heparinized sample of blood in Wintrobe tubes at 3,000 rpm for 55 minutes. Paired arterial and venous blood gases were determined with the Radiometer Acid Base Analyzer (Copenhagen PHM 71) and oxygen saturation using an Instrumentation Laboratory cooximeter Model 182. Pyruvate and lactate levels were measured.[10,15] Arterial samples were used to plot three points on the oxyhemoglobin dissociation curve and to calculate the P50.[32] 2–3 DPG,[17,18] total protein, albumen (modified Biuret method) and serum phosphorus by the Autoanalyzer were also measured. A right angle Ingold pH probe and Corning pH meter were employed to monitor muscle surface pH.[1] Cardiac output (CO) was measured by the thermodilution technique.[7] At each measurement, five readings were obtained and the mean was computed. A baseline sample was drawn

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[*] Plasmanate (Cutter) contains 5% protein, mainly albumen, in 0.15M conc saline.

TABLE 2. *Cardiovascular Effects of Hemodilution*

		Baseline	Hemodil. I	Hemodil. II	Mid Op	Post Op
Cardiac Output ml/min						
	ML	2714	3744	4302		3387
	SM	5008	5822	7200	5980	7150
	RH	3207	4121	3334	4577	4843
	SP	5209	5800	7184	5891	5031
	Mean	4034	4871	5505	5482	5102
	±SEM	629	547	993	453	775
Arterial Blood Pressure						
	Mean	122/78	117/80	115/76	115/80	119/76
Central Venous Pressure						
	Mean	14.5	16.3	17.3	13.0	12.8
Pulmonary Artery Pressure						
	Mean	21/14	22/16	24/16	18/9	19/10
Heart Rate						
	Mean	83	80	83	80	73

to measure ^{51}Cr tagged RV. BV was then calculated as follows:

$$BV = \frac{RV}{LVH \times TBH}$$

where RV equals red cell mass and TBH equals total body hematocrit. TBH was calculated from the RV and PV measured the day pre-operatively. After Hemodilution I and II the quantity of shed blood was measured and samples drawn to measure the ^{51}Cr tagged RV. BV after Hemodilution I and II was then calculated using the TBH-to-LVH ratio measured preoperatively. In three patients the ^{51}Cr tagged RV and Evans' blue dye PV were measured on the first postoperative day.

Results

Cardiovascular Effects

Results of step-wise hemodilution with replacement of BV are shown in Table 2. Mean hematocrit after Hemodilution I was 29.3% and after Hemodilution II 21.5%. At midoperation hematocrit was 19.7%, at end of operation 25.7% (Table 3). Mean volume of blood withdrawn was 1975 ml. RV was reduced by 21.6% after Hemodilution I and 21.5% after Hemodilution II. The most striking cardiovascular effect was a rise in CO to a mean of 123.5% after Hemodilution I and 136.3% after Hemodilution II. At mid-operation CO was 124% and at end of operation 129%. With a slight fall in pulse rate, calculated stroke volume increased. Radial artery, central venous, pulmonary artery, and pulmonary artery wedge pressures remained unchanged. Calculated total peripheral resistance was reduced, to 80% after Hemodilution I and to 73% after Hemodilution II. By the end of hemodilution there was a mean reduction of temperature of 1.5 C.

Oxygen Transport

Paired arterial and central venous gases are shown in Table 1. With reduction in hemoglobin there was a decrease in oxygen carrying capacity and no increase in the arterio-venous oxygen content difference (AVO_2D) following hemodilution. Instead the AVO_2D decreased slightly as depicted in Fig. 2 and Table 1. However, at end of operation the AVO_2D had increased. This may have been the result of returning consciousness and increased muscular activity. Also intravascular volume may have been reduced at this time. The calculated systemic oxygen transport (SO_2T) (CO in ml/min × arterial oxygen content in ml/min) was slightly reduced after Hemodilution I to 88% and after II to 83%, a small reduction as compared to the reduction in oxygen carrying capacity, to 70% and 54.5% as shown in Fig. 3.

2–3 D.P.G. level, after so short a time, remained unchanged. One patient who received one unit of bank blood which contains reduced amounts of 2–3 D.P.G. had

TABLE 3. *Acute Hemodilution: Changes in Hematocrit*

		Day Pre-Op	Baseline	After Hemodil. I	After Hemodil. II	Mid Op	End of Op
LVH%							
	ML	45.9	38.9	28.5	23.2	20.0	33.5
	SM	47.3	44.4	33.9	19.8		21.8
	RH	49.2	48.3	28.6	22.5	20.5	24.9
	SP	38.2	36.5	26.0	20.8	18.6	22.6
	Mean	45.2	42.0	29.3	21.5	19.7	25.7
	±SEM	2.4	2.66	1.7	0.7	0.57	2.7

a reduced level at the end of operation. Measurement of the P50 showed no change in the position of the oxyhemoglobin dissociation curve.

Tissue Perfusion

Pyruvate and lactate levels remained unchanged during and after hemodilution. However at the end of operation, both values were elevated, the pyruvate-lactate level remaining unchanged.

Muscle surface pH showed a consistent rise after each hemodilution, approaching the pH of arterial blood. This was thought to be due to increased blood flow (Fig. 4). The large rise in muscle surface pH seen at mid-operation is thought to be due to positional change of the probe caused by moving the patient.

Blood Volume

Results of BV studies are shown in Table 4. As can be seen, at the time of baseline measurements, there was an increase in BV of 12% as compared to the day preoperatively. This was associated with a rise in plasma volume, and an appropriate fall in hematocrit, from a mean of 45.2% preoperatively, to 42.0% at the first measurement. Similar increases in BV have been described with halothane anesthesia. There was also an increase in BV after Hemodilution I and II. These were calculated however from the measured RCM and LVH, using the TBH-to-LVH ratio measured preoperatively. It is possible that this ratio changes under the conditions of hemodilution. In three patients BV measurements done one day postoperatively by the ^{51}Cr and Evans' blue dye method showed a mean value of 89.8% as compared to the preoperative volume.

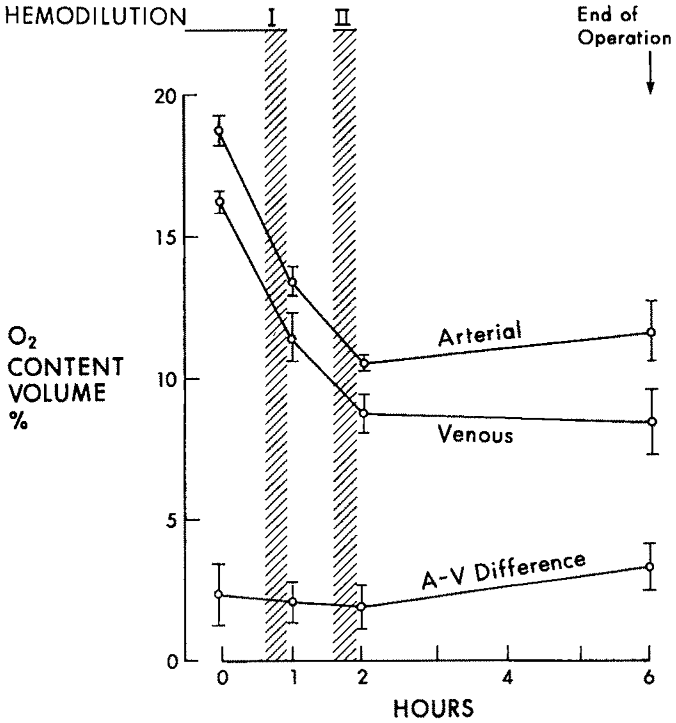

FIG. 2. The arterial and venous oxygen content difference with hemodilution and at the end of operation. Note the slight reduction in AV O_2 difference after each step in hemodilution shown in the bottom line. The vertical lines indicate the SEM.

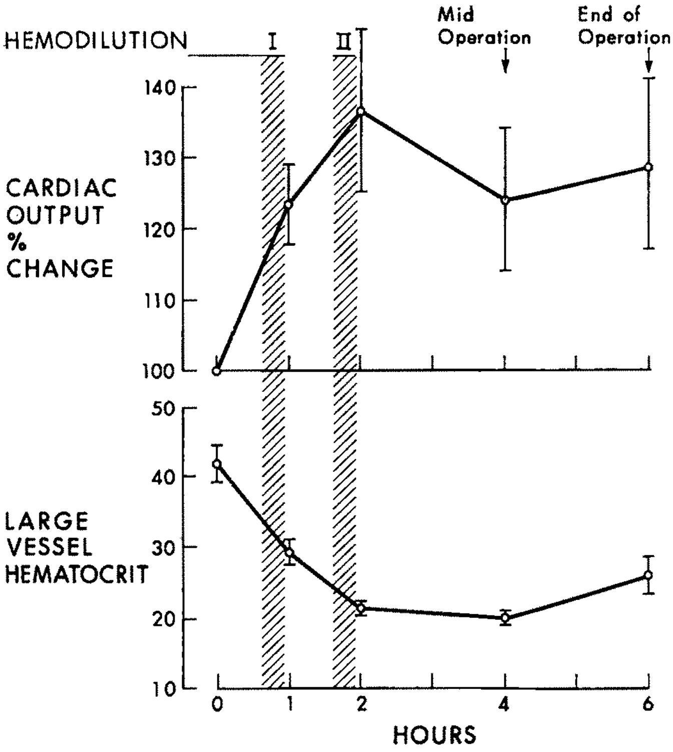

FIG. 1. Change in CO with reduction in hematocrit after hemodilution I and II. Vertical lines represent standard error of the mean (SEM). After hemodilution I: CO was 125%, Hct 29%. After hemodilution II: CO was 136% and Hct 21.5%.

Discussion

Acute hemodilution with BV replacement resulted in an increase in CO (Fig. 1). As the pulse rate remained stable, the increase in CO was largely the result of an increase in stroke volume (SV). There are several possible explanations for the increase in CO. These include the possible effects of fluoroxene anesthesia, hypovolemia, a decrease in tissue oxygenation, and the action of catecholamines or the autonomic nervous system. The most acceptable explanation however is the effect of hemodilution on viscosity and peripheral resistance.

Cullen *et al.*[2] showed that fluoroxene administered to volunteer subjects for 90 minutes at concentrations of 5 and 9% had no effect on CO, although causing a slight rise in CVP. The addition of nitrous oxide to 5% fluoroxene anesthesia produces an alpha-adrenergic sympathomimetic response and does not increase CO.[31] In the present study, with a mean concentration of fluoroxene of 5%,

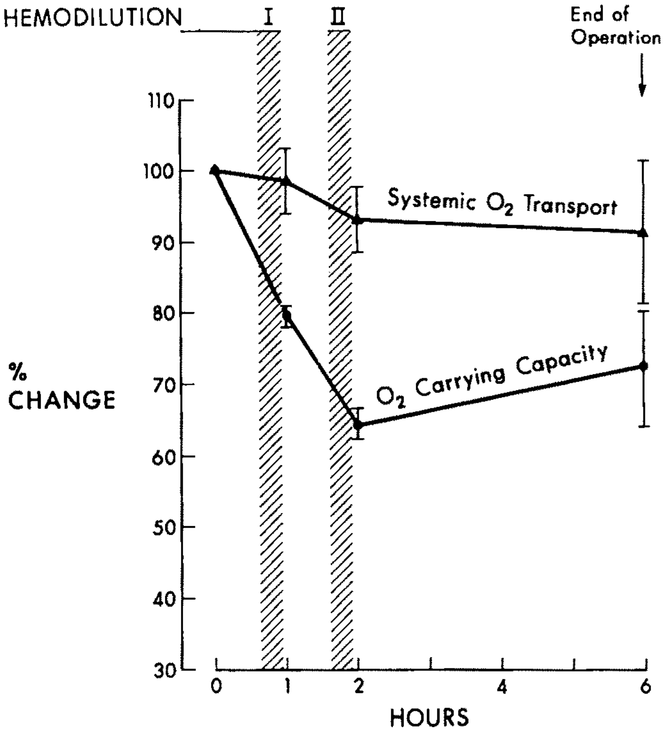

FIG. 3. The effects of hemodilution on muscle surface, arterial and venous pH. Note the slight rise in muscle surface pH after each step of hemodilution. The rise in muscle surface pH seen at mid-operation is thought to be due to positional changes of the probe caused by moving the patient.

cardiovascular effects cannot be ascribed to the anesthetic agent.

Glick *et al.*[9] studied the effects of hemodilution on hemodynamics in nonanesthetized dogs, with and without cardiac autonomic denervation. In the denervated dog, CO rose but to a lesser degree as compared to the intact animal. Also, the rise in CO in the denervated animals resulted from an increase in SV rather than in increase in HR as occurred in the intact animals. It is of interest that in our group of patients under the influence of anesthesia, the major effect was also a rise in SV rather than an increase in HR.

As shown in Table 4, BV increased after Hemodilution I and II as calculated from RV, LVH, and the LVH-to-TBH ratio. Changes of BV of this magnitude (10–20%) however have been shown to have little effect on CO.[6,30,33] Schnabel *et al.*[30] found that increases of blood volume of 22.5% were associated with a rise in CO. This was accompanied however by a rise in right atrial pressure of 242%. Right atrial and pulmonary capillary wedge pressures remained stable in the present study making hypervolemia an unlikely explanation for the rise in CO. Fowler *et al.*[5] also showed that there was no increase in CO associated with similar degrees of anemia in hypervolemic as compared to normovolemic experimental animals. Murray *et al.*,[24] on the other hand, showed that with hypervolemia CO was greater than that for equivalent degree of anemia at normovolemia. In their study however BV was expanded by about 50% and was associated with a rise in right atrial pressure.

It is unlikely that a decrease in PO_2 and tissue oxygenation was responsible for the increase in CO. Indicators of tissue perfusion, muscle surface pH, venous pH, PO_2, and PCO_2, pyruvate, and lactate levels remained unchanged or improved, making this explanation unlikely. It has also been found in the dog that 3 atmospheres of oxygen, which restores arterial oxygen content to prehemodilution level, does not abolish the rise in CO.[4] Likewise, Messmer *et al.*[20] showed that hemodilution did not cause a decrease in local oxygen tension in different organs using a tissue PO_2 electrode.

Rheologic studies done by others[19,21,28] have demonstrated a parallel decrease in total peripheral resistance and whole blood viscosity with progressive hemodilution. Guyton and Richardson[13] demonstrated that the decrease in peripheral resistance resulted in increased venous return and thus increased CO. Reduced viscosity resulting from hemodilution may play a major role in increasing the CO.

In the presence of hypovolemia, hemodilution causes a lesser increase in CO.[21] Watkins *et al.*,[34] studying gradual hemorrhage in normal volunteers found that the major compensatory response was an increase in oxygen extrac-

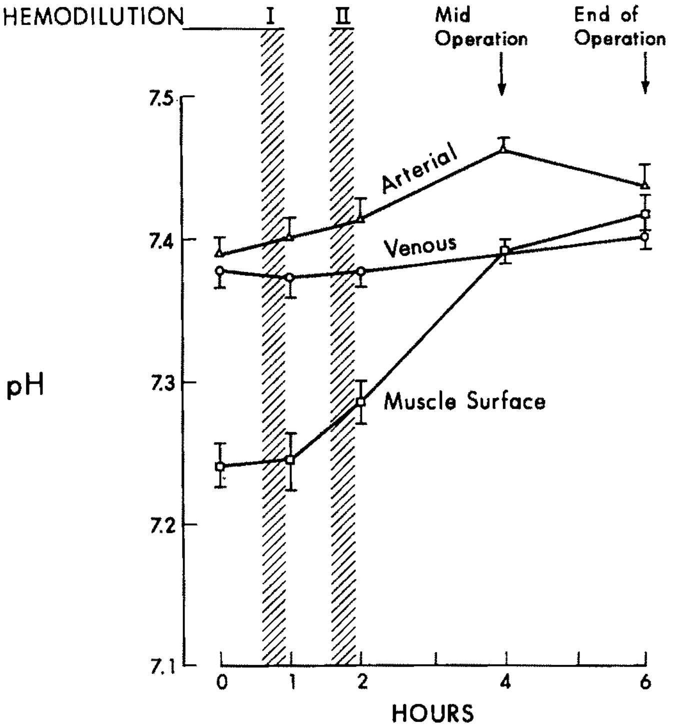

FIG. 4. The changes in systemic oxygen transport (SO_2T) and oxygen carrying capacity (O_2CC) with hemodilution. As O_2CC falls to 70% and 54.5% after hemodilution I and II the SO_2T falls to 88% and 83%.

TABLE 4. *Changes in Blood Volume with Hemodilution*

		Day Pre-Op	Baseline	After Hemodil. I	After Hemodil. II	Day Post-Op
BV						
	ML	3664	4469	4710	5166	3594
	SM	4989	5543	6024	8131	3959
	RH	4143	4351	5238	5533	3812
	SP	3671	4112	4437	4816	
	Mean	4117	4618	5102	5911	3788
	±SEM	312	316	349	754	106
RV						
	ML	1619	1669	1293	1141	1214
	SM	2104	2191	1812	1433	794
	RH	1743	1804	1288	1070	977
	SP	1171	1261	969	842	
	Mean	1659	1731	1341	1122	995
	±SEM	192	192	174	122	122
PV						
	ML	2045				2380
	SM	2885				3165
	RH	2400				2835
	SP	2500				
	Mean	2458				2793
	±SEM	173				228

tion ratio and that CO did not increase. This may be explained by a reduction in BV caused by the repeated phlebotomy without adequate replacement. In studies of normovolemic hemodilution in experimental animals[8,19,21,23] there was no significant increase in AV oxygen difference. In the present study the AVO_2D fell as shown in Fig. 2. This underscores the importance of maintaining BV in the presence of acute reductions in hematocrit.

Systemic oxygen transport is the amount of oxygen carried in the systemic circulation per minute and is calculated from COX arterial O_2 content. In hemodilution because of the reduction in oxygen carrying capacity, systemic oxygen transport will remain constant only if there is a compensatory rise in CO. In this study there was a slight decline in SO_2T after each step of hemodilution (Fig. 3). Because of the compensatory increase in CO however, this was far less than the reduction in O_2 carrying capacity.

There has been controversy over the concept of the ideal hematocrit, i.e. the hematocrit at which CO and O_2 carrying capacity are so balanced as to result in a maximum SO_2T. This is dependent on BV to some extent and may explain the difference in results obtained in several related studies. Guyton[13] and Gump,[12] using lactated Ringer's solution as the hemodiluting agent, found a stepwise fall in oxygen transport capacity and concluded that 40% was the "ideal hematocrit." Messmer *et al.*,[19,21] using Dextran, found that the increase in CO "over compensated" until a hematocrit of 30% was reached, concluding that 30% was the ideal hematocrit in the dog. This was not substantiated by Murray *et al.*, who also gave Dextran in dogs.[23] In our study, reduction of hematocrit to a mean of 29.3% then 21.5% was associated with a stepwise slight fall in systemic O_2 transport (Fig. 3).

Despite the small reduction in SO_2T, tissue perfusion and oxygenation remained excellent. Muscle surface pH increased with stepwise hemodilution and tended to approximate the arterial levels (Fig. 4). This may be explained by the increase in blood flow to the skeletal muscle which has been shown to occur with experimental hemodilution.[19,26] Likewise central venous pH rose and the central venous pyruvate, lactate and pCO_2 remained unchanged.

The patients studied tolerated the procedure well. Because of the infusion of lactated Ringer's solution, the patients had a diuresis both intra- and postoperatively. Mean blood loss was 2,500 ml. During the first half of the procedure, blood loss was replaced with lactated Ringer's solution and plasmanate. In the second half of the procedure, just after measurements had been made, the patients' own blood was reinfused. This sufficed for intraoperative requirements in all patients except one in whom an additional unit of bank blood was required intraoperatively. There were no postoperative complications in this group of patients.

This study has shown that the major compensatory factor in acute normovolemic hemodilution is an increase in CO and that hemodilution to hematocrit levels of 21% was well tolerated in these patients anesthetized with fluoroxene for total hip replacements. Effective compensation is dependent on cardiac, pulmonary and renal function, and patients with diseases of these systems were excluded from hemodilution. It is not known whether these findings can be extrapolated to other situations such as acute trauma or burns.

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Use of the Umbilical Vein to Study the Splanchnic and Portal Beds in Shock and Trauma:

II. Metabolic Studies

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Perumbilical portal vein catheters and arterial and central venous catheters were inserted in 16 patients recovering from trauma or other shock-producing events, and in 5 patients who later developed shock. This permitted serial measurement of blood gases, pH, and the levels of ammonia, lactate and certain other metabolites in all three circulatory systems simultaneously. Nine of the trauma patients were never in shock, had no liver disease or injury and consequently formed a baseline group for comparison with the shock patients. In the shock patients there was a significant degree of hypoxemia in the portal venous blood and an increase in the arterial-portal oxygen saturation difference. Their portal venous blood showed a lower pH and a higher pCO_2 than did the portal blood of the patients who had never been in shock. In 3 of the 4 shock patients who died, the total blood lactate showed a greater increase in portal venous than in the arterial or central venous blood. In shock there was also an increase in portal venous blood ammonia which was later accompanied by increments in arterial and central venous blood ammonia. This suggests impairment of hepatic urea synthesis, allowing escape of ammonia through the liver. These phenomena, when added to the finding previously reported of an elevated portal venous pressure in some shock patients, lend support to the hypothesis that in certain cases of shock there is increased impedance to flow of portal blood through the liver with resultant stasis in the portal-splanchnic bed and ischemic-hypoxic hepatocellular injury.

STUDIES IN CANINE HEMORRHAGIC SHOCK have demonstrated marked changes in the portal venous pressure and in the ammonia levels of mixed systemic venous, arterial, and portal venous blood samples.[5,9] Other investigations[4,6,16,17] have indicated that the liver plays a vital role in shock and may be the site of changes which lead to irreversibility. An analysis of the autopsy findings in 53 patients who died in shock showed the predominant morphological change at light microscope level was in the liver.[4]

The introduction by Gonzalez-Calbalhaes[7] and Bayly[1] of portal vein cannulation via the reopened umbilical vein provided a new technique for the study of the liver and its circulation. In a previous report[10] we described the use of the technique for manometric and radiographic studies of the splanchnic-portal system in a series of shock and trauma patients.

This report presents the results of metabolic studies performed by the method in shocked and non-shocked traumatized patients. Routinely placed arterial and central venous catheters allowed simultaneous sampling to compare levels of blood gases and metabolites in the portal vein with levels in the systemic circulation.

Methods

Twenty-one patients admitted to the Maryland Institute for Emergency Medicine were included in the study. They were subdivided as follows: Nine trauma patients who had never been in shock (Non-shock Group); seven patients who had been in shock but who had been successfully resuscitated (Shock-Trauma Recovery Group); and five patients studied during shock (Shock Group). The portal venous pressure changes in the last group were described in a previous report.[10]

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In all patients, the portal vein was catheterized via the umbilical vein, and the routine arterial and right atrial catheters were inserted. The arterial lines were inserted by a percutaneous stab of the femoral artery. Simultaneous blood samples were taken from these three lines for analysis at six-hourly intervals from the time of admission until stabilization or death.

The nine patients placed in the Non-shock Group fulfilled the following criteria: 1) an exploratory laparotomy had been performed because of actual or suspected abdominal trauma; 2) absence of significant hepatic or splenic injury; 3) absence of liver disease (based on visual appearance, liver function tests and in many cases, a biopsy); and 4) no period of shock.

The following determinations were made on the six-hourly blood samples:

1.pO_2, pCO_2, and pH (using the IL 313 Analyzer).

2. Oxygen saturation, standard bicarbonate and base excess using the Sigaard-Andersen Nomogram.

3. Oxygen content using the formula O_2 (mls/100 ml = ($pO_2 \times 0.003$) + (Hb (gms) $\times$ 1.39 $\times$ O_2 Sat. %).

4. Hemoglobin (Cyan methemoglobin) and hematocrit (microcentrifuge).

5. Blood urea nitrogen (urease method, the colorimetric Harnstoff-Farb technique.

6. Blood ammonia (indophenol technique).

7. Total blood lactate (Boehringer Mannheim Ultraviolet Enzymatic Spectrophotometer).

TABLE 1. *Comparison of Mean-Blood Levels from Non-shock and Shock Groups*

	Non-Shock Group			Shock Group		
Variable	Number of Patients	Mean	Variance	Number of Patients	Mean	Variance
Art. O_2 Content	7	18.0	2.11	5	15.1	28.6
Port. O_2 Content	7	16.4	1.62	5	12.6	26.1
Ven. O_2 Content	7	14.2	2.36	5	10.3	32.1
A-P Diff.	7	1.59	1.40	5	2.44	0.68
P-V Diff.	7	2.15	0.42	5	2.35	0.36
Art. O_2 Saturation	7	95.5	0.952	5	93.0	18.5
Port. O_2 Saturation	7	86.9	18.2	5	77.0**	24.5
Ven. O_2 Saturation	7	76.5	22.0	5	58.0†	321.5
A-P Diff.	7	8.52	23.5	5	16.0*	42.0
P-V Diff.	7	10.4	11.8	5	19.0	214.5
Art. PCO_2	7	33.7	22.3	5	34.2	45.2
Port. PCO_2	7	34.8	23.7	5	41.0*	50.0
Ven. PCO_2	7	38.3	27.9	5	44.0	80.5
A-P Diff.	7	−1.04	1.42	5	−6.80	129.2
P-V Diff.	7	−3.48	1.57	5	−3.00	33.5
Art. PH	7	7.459	0.00087	5	7.395*	0.0050
Port. PH	7	7.446	0.00069	5	7.324†	0.0093
Ven. PH	7	7.223	0.00071	5	7.308**	0.0055
A-P Diff.	7	0.0131	0.00009	5	0.071	0.0102
P-V Diff.	7	0.0227	0.00015	5	0.016	0.00069
Art. Base Excess	7	0.992	2.67	5	−3.04	31.4
Port. Base Excess	7	0.840	2.76	5	−4.02	29.0
Ven. Base Excess	7	0.908	2.46	5	−3.78	32.7
A-P Diff.	7	0.152	0.52	5	0.980	2.40
P-V Diff.	7	−0.068	0.83	5	−0.240	4.13
Art. Lactate	8	1.08	0.193	5	12.6	183.9
Port. Lactate	8	1.11	0.211	5	14.3	225.5
Ven. Lactate	8	1.17	0.098	5	12.6	143.5
A-P Diff.	8	−0.020	0.0068	5	−1.76	4.66
P-V Diff.	8	−0.046	0.0407	5	1.72	11.7
Art. NH_3	7	1.13	0.177	4	1.31	0.097
Port. NH_3	7	1.83	0.165	4	3.03	1.75
Ven. NH_3	7	1.05	0.186	4	1.10	0.073
A-P Diff.	7	−0.699	0.127	4	−1.71	1.17
P-V Diff.	7	0.786	0.136	4	1.92	1.13

A-P Diff = Arterial-Portal Venous Difference

P-VDiff = Portal Venous-Central Venous Difference

Legend:
Student's t-test
* $p < 0.05$
** $p < 0.01$
Modified t-test
† $p < 0.05$

Because of the increase in the arterial-portal oxygen difference which accompanies oral intake of food, only those patients on parenteral alimentation were included in the study.

Many patients received oxygen inhalation therapy in their postoperative care, and this tended to raise the PaO_2 above normal. In this study the normal range for PaO_2 was considered to be 60–110 mm Hg. When the PaO_2 was outside this range, all the blood gas results for that sampling period were discarded. Blood ammonia values were excluded in two patients because of blood present in the intestinal tract.

In patients with several sets of determinations, the mean was obtained and considered as equal in value with the result in patients having only one determination in arriving at the overall mean. This was done because preliminary analysis of variance suggested that the non-shocked patients were not biochemically identical. Variation between patients was greater than the variation between the results of different sampling periods in the same patient.

In those patients who died in the Shock Group the last complete blood study before death was analyzed, and in the patient who survived, the sample at the time of most severe shock was used. All five patients were being mechanically ventilated with oxygen-enriched gas mixtures at the time the samples were drawn.

Results

The Non-Shock Group

The results in this group are shown in Table 1.

The oxygen content and saturation of the portal venous blood were intermediate between those of the arterial and central venous blood, as was the pCO_2 and PH. There was no significant difference between arterial, portal, and central venous levels of standard bicarbonate, base excess, total blood lactate or blood urea nitrogen. Portal venous ammonia, with a mean of 1.8 µg/m, averaged 80% higher than arterial and central venous ammonia levels.

The Shock Trauma Recovery Group

The blood gas results in this group did not differ significantly from those of the Non-shock Group. The patient who resumed oral intake of food during the studies showed an increase in the arterial-portal oxygen content difference (Fig. 1).

The main differences between the Shock-Trauma Recovery Group and the Non-shock Group related to the blood lactate and blood ammonia levels.

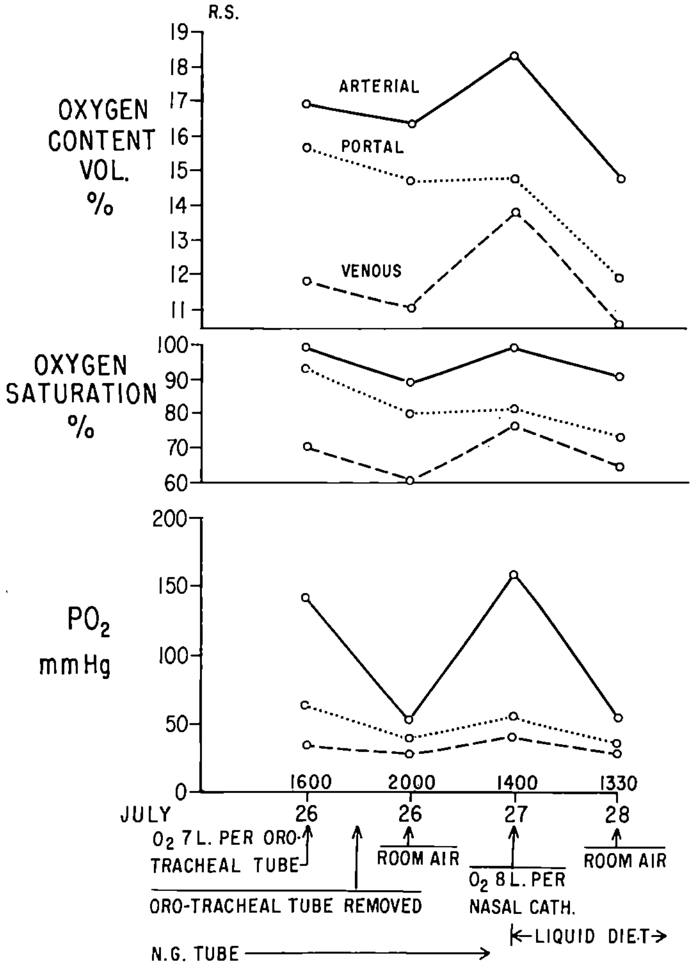
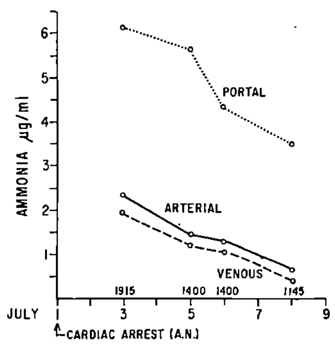


FIG. 1. Patient R. S. of Shock-Trauma Recovery Group. Arterial, central venous and portal oxygen levels following thoracotomy for stab wound of the chest. Elevations of arterial PO_2 produced by oxygen inhalation therapy are reflected in smaller elevations of portal and central venous PO_2. When oxygen content and saturation are graphed the portal curve initially lies closer to the arterial than to the venous. After the patient resumed oral intake, the arterio-portal oxygen difference increased.

Using a previously established upper normal limit for total blood lactate of 1.5 mEq/l or 13 mg/100 ml, eight Shock Trauma Recovery patients had elevated levels on admission ranging from 2.70 to 8.05 mEq/l, with no significant difference being noted between the different sites of blood sampling. The lactate level correlated closely with the severity of trauma and with the extent and duration of the patient's hypotension. The

FIG. 2. Portal, central venous and arterial ammonia curves in A. N., a 33-year-old female in the Shock-Trauma Recovery Group, following resuscitation from cardiac arrest due to rheumatic heart disease.



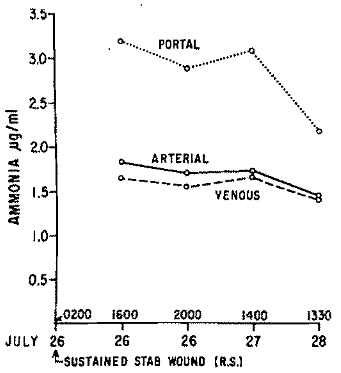


Fig. 3. Comparative ammonia curves in the same patient whose course is illustrated in Fig. 1. In both Figs. 2 and 3, all three curves decline toward normal as the patients recover, but the rate of descent of the portal ammonia curve is more rapid than that of the arterial and venous curves.

two Shock Trauma Recovery patients who had experienced major shock-producing events, namely, a cardiac arrest (Fig. 2) and a stab wound of the chest with hemopneumothorax (Fig. 3), produced substantially raised initial ammonia levels in the portal as well as the arterial and central venous blood. As the patients improved, the ammonia levels from all three systems gradually decreased with the portal ammonia level remaining at least double that of the central venous reading despite a greater rate of fall.

The ammonia levels in five other patients who had been in various degrees of shock were elevated but to a lesser degree.

No significant differences between the three circulatory systems were found in the other parameters measured.

The Shock Group

The mean value and variance for each parameter are shown in Table 1. In comparing the means of the Shock Group with those of the Non-Shock Group, the differences between the means were tested for statistical significance using a one-tailed Student's t-test, taking into account gross inequalities ($p \leq 0.01$) of variances

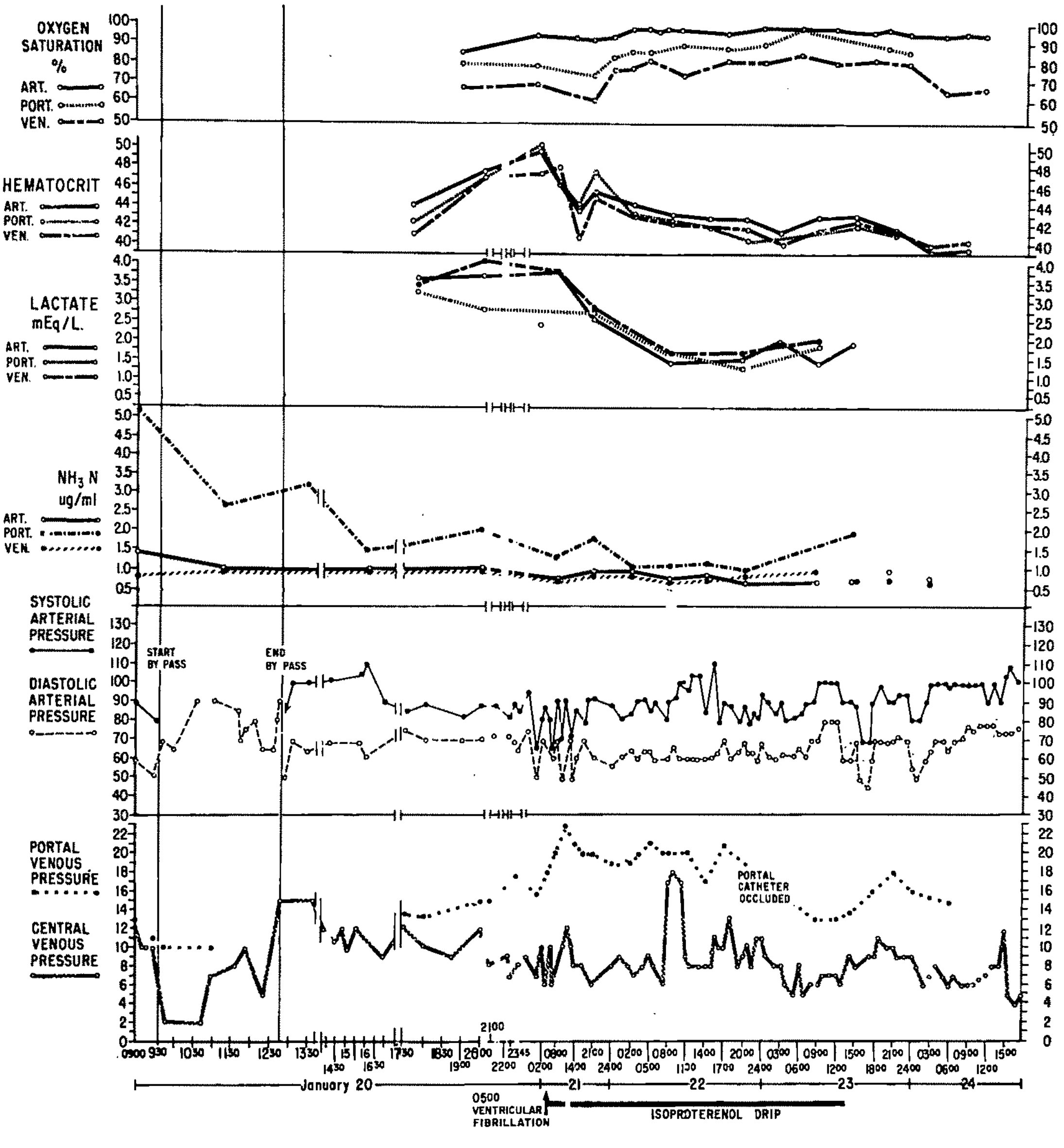


Fig. 4. Patient C. U. of the Shock Group, who developed unexplained shock and ventricular fibrillation following cardiopulmonary bypass despite replacement of blood and fluid losses. Shock was accompanied by rising portal venous pressure (PVP) and declining central venous pressure (CVP). Administration of isoproterenol was followed by a gradual return of arterial, portal and central venous pressures toward normal. The initial elevation of blood lactate may have been due in part to the Ringer's lactate used in the hemodilution perfusion.

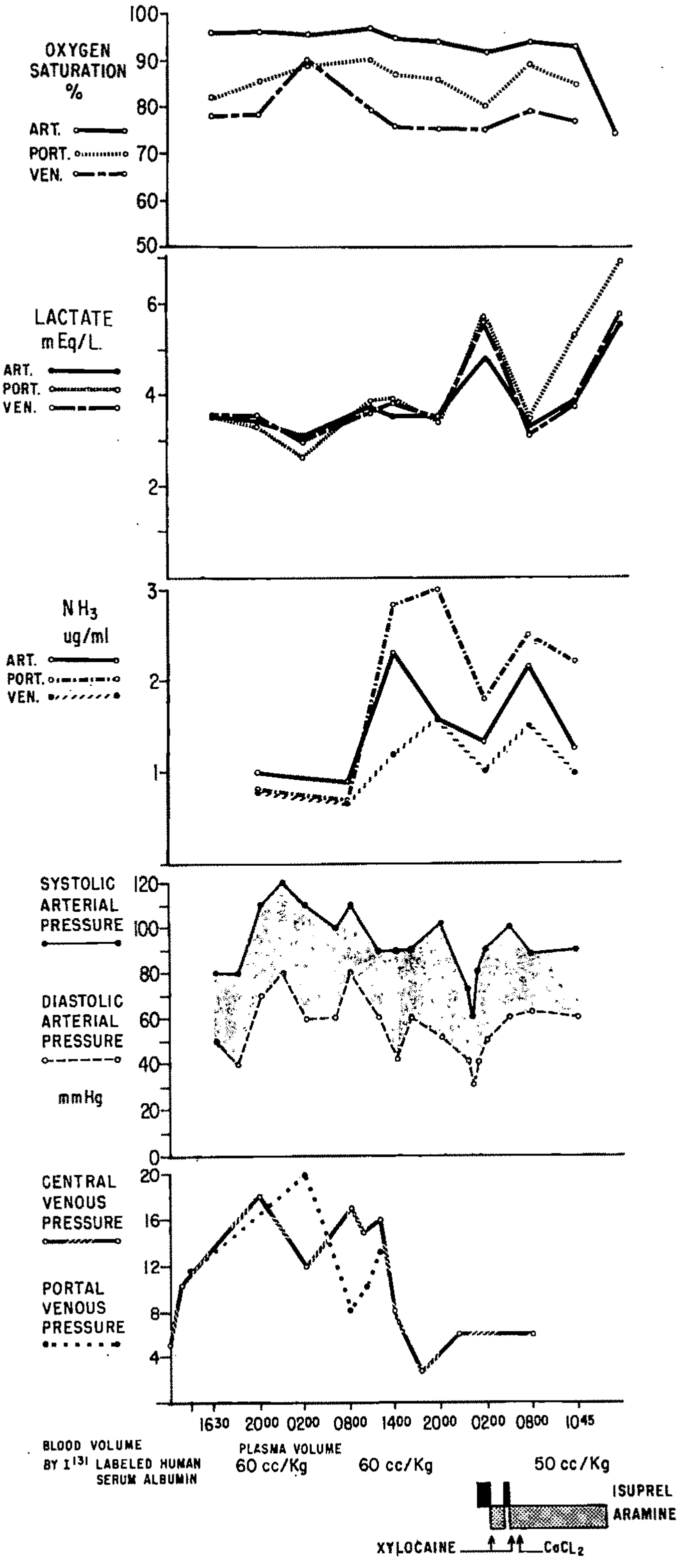


FIG. 5. C. A., a 50-year-old man with hypovolemic and bacteremic shock (Bacteroides) resulting from complications of a thoracoabdominal gunshot wound sustained on 10/08/69. The umbilical catheter was inserted during a laparotomy performed to control delayed bleeding from the diaphragm on 10/21/69. The patient expired in refractory shock on 10/23/69. C. A. and patient M. D. (Fig. 8) are the two patients from the Shock Group in whom the PVP and CVP curves did not diverge.

where necessary by using the modification given by Brownlee.[3] Failure to find a statistically significant difference between the Shock and Non-shock patients in

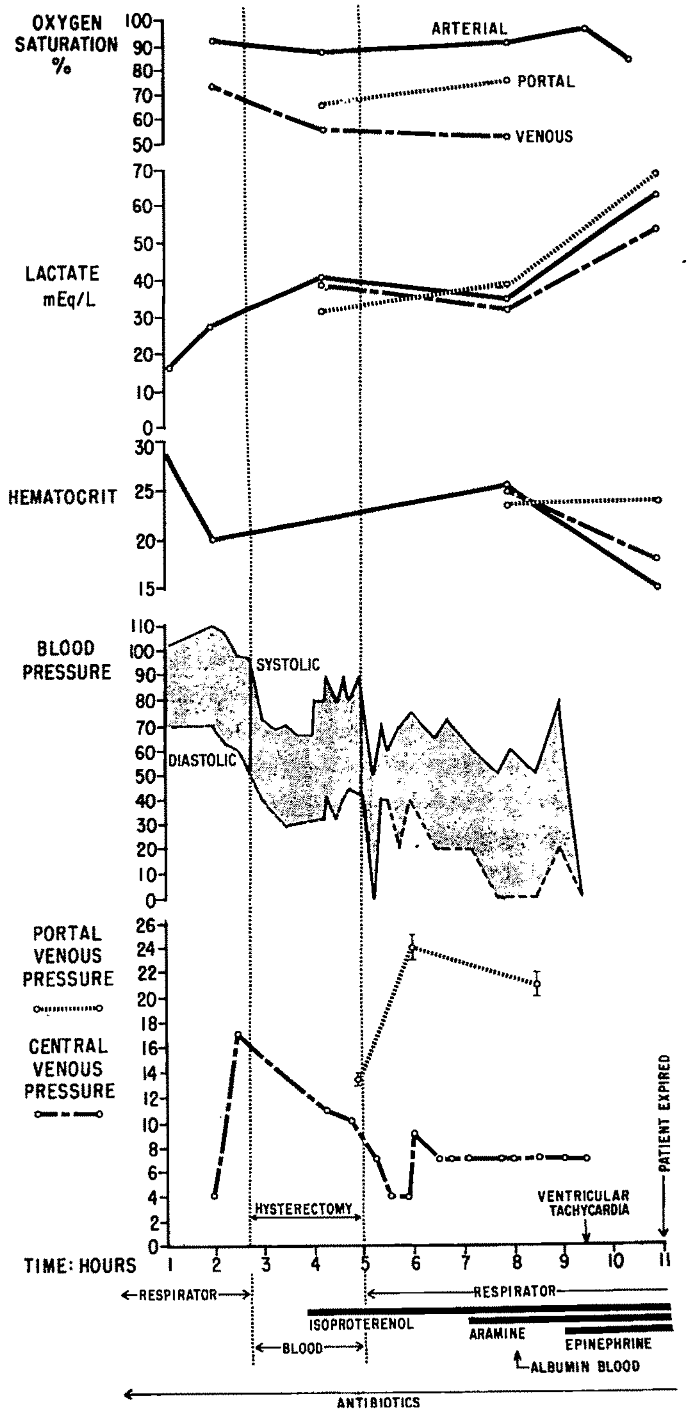


FIG. 6. B. B., a 35-year-old female with bacteremic shock (Enterococcus) due to septic abortion with gas in the uterus in whom hysterectomy and bilateral salpingo oophorectomy failed to reverse the shock process. The patient also failed to respond to volume replacement, isoproterenol, metaraminol, and epinephrine. Note the divergence of PVP and CVP curves and the slight rise in portal hematocrit while the arterial and venous hematocrits were falling, due to hemorrhagic diathesis with intraperitoneal bleeding.

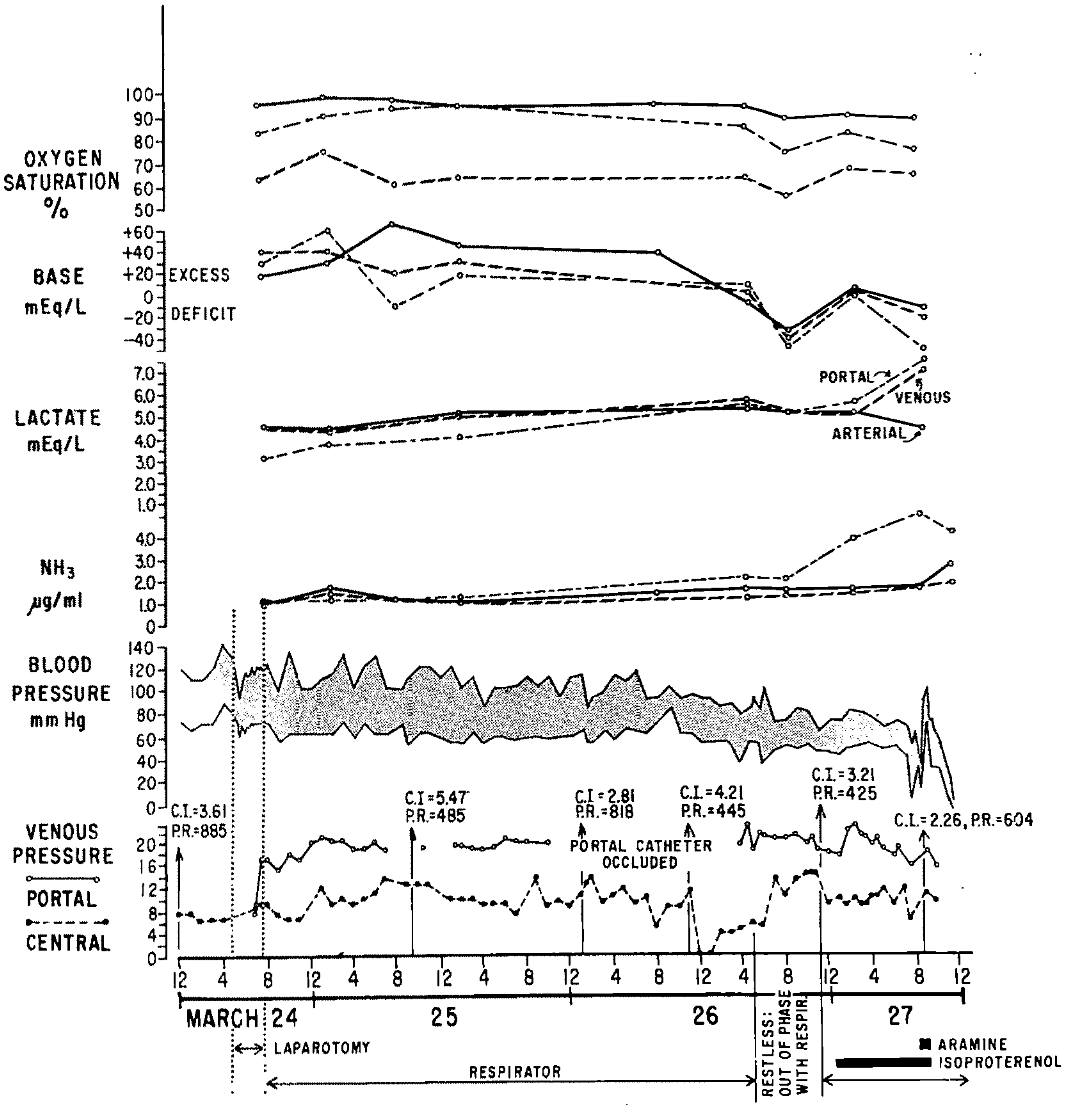


FIG. 7. W. L., a 55-year-old man who developed fever, hypotension and oliguria six days following gastrectomy for bleeding duodenal ulcer performed on 3/16/70. Laparotomy on 3/24/70 revealed a partially transected pancreas with pancreatic ascites. The pancreatic capsule was repaired and the pancreas drained. Liver biopsy showed extensive central and mid-zonal necrosis. Two days postoperatively, hypotension and oliguria accompanied by low central venous pressure ensued which were unresponsive to apparently adequate volume replacement. Note that divergence of portal and central venous pressures and increased arterio-portal oxygen saturation difference developed at this time, before any vasopressors were given.

parameters other than those where this is shown may simply be the result of small sample size.

Blood Gases. Oxygen saturation measurements were more meaningful than oxygen content because significant anemia in two shock patients (B.B. and M.D.) materially affected the latter. The portal venous oxygen saturation declined below the mean value for the Non-Shock Group of 86.9% (Table 1) in four of the five shock patients (Figs. 4–8). The fifth patient, C.A., had a preterminal oxygen saturation of 85% although it had been only 80% eight hours earlier. In patients W.L. and B.B., the low portal venous oxygen saturation was associated with a low arterial oxygen saturation (87% in W.L. and 92% in B.B.), but in patient M.D., the low portal saturation (73%) occurred despite an arterial oxygen saturation of 100%. The mean portal venous oxygen saturation for the Shock Group (Table 1) was 77.0%, in contrast to 86.9% in the Non-shock Group ($p < 0.01$). The mean arterial-portal oxygen saturation difference in the Shock Group was 16.0%, compared to a mean of 8.52% for the Non-shock Group ($p < 0.05$).

The failure to find a significant difference in the oxygen content values between the Non-shock and Shock groups was related to the presence of anemia in two of the shock patients. The hemoglobin was 9.0 grams in B.B. and 5.0 grams in M.D. The oxygen content of blood from all three circulatory systems in these two patients was therefore much lower than in the remaining three, and the variance for the Shock Group was consequently great.

The mean portal venous PCO_2, though intermediate between the arterial and central venous levels as in the Non-shock Group, was higher in the Shock Group ($p < 0.05$).

The mean pH of the blood from all three systems was significantly lower in the Shock Group ($p < 0.05$ for arterial and portal venous pH and < 0.005 for central venous pH). The mean arterial-portal pH difference appeared greater in the Shock Group than in the Non-shock Group but a statistical difference could not be shown at the $p < 0.05$ level. The greater acidity of portal venous blood in the Shock Group also appeared to be reflected in the mean base deficit which was 4.02 mEq/l compared to a mean base excess of 0.84 mEq/l for the Non-shock Group. This difference, though not significant at the 0.05 level, was very nearly so. T-statistic here = 1.95. T = 2.015 at 5 degrees of freedom is significant at the 0.05 level.

Total Blood Lactate. In the survivor (C.U.) of the Shock Group no significant difference was observed between arterial, central venous, and portal venous lactates although the values following surgery and an episode of ventricular fibrillation had been up to 4 mEq/l before gradually returning to normal (Fig. 4).

In the four patients who died in refractory shock, there was a progressive increase in both portal venous and systemic lactate levels and in the final samples, three of these patients (W.L., C.A., and B.B.) showed a substantially higher lactate level in the portal vein (Figs. 5–8). It is interesting that the fourth patient (M.D.) did not show a widened portal venous pressure-central venous pressure gradient.[10]

Ammonia. Serial ammonia determinations were performed in four shocked patients. The survivor (C.U.), showed raised portal venous ammonia levels before, during and immediately after cardiopulmonary bypass (Fig. 4) which thereafter did not rise above 2.0 μg/ml. The arterial and central venous ammonia levels did not exceed 1.0 μg/ml throughout this period.

In the remaining three shock patients (W.L., M.D., and C.A.), the portal ammonia reached peaks of 4.9, 4.6, and 3.0 μg/ml respectively. In each case there were significant, though lesser, elevations of arterial and central venous ammonias (Figs. 5, 7, and 8).

Discussion

The results indicate that during shock important changes occur in the levels of certain substances in portal venous blood and in the relationships between portal venous and systemic blood levels of these substances. An analysis of these changes may improve our understanding of some basic pathophysiologic mechanisms in shock.

In order to obtain a baseline against which to compare the shock patients, it was necessary to accumulate data on "controls" (non-shocked patients) since the literature contains relatively little information regarding the chemical constituency of portal venous blood in normal humans.

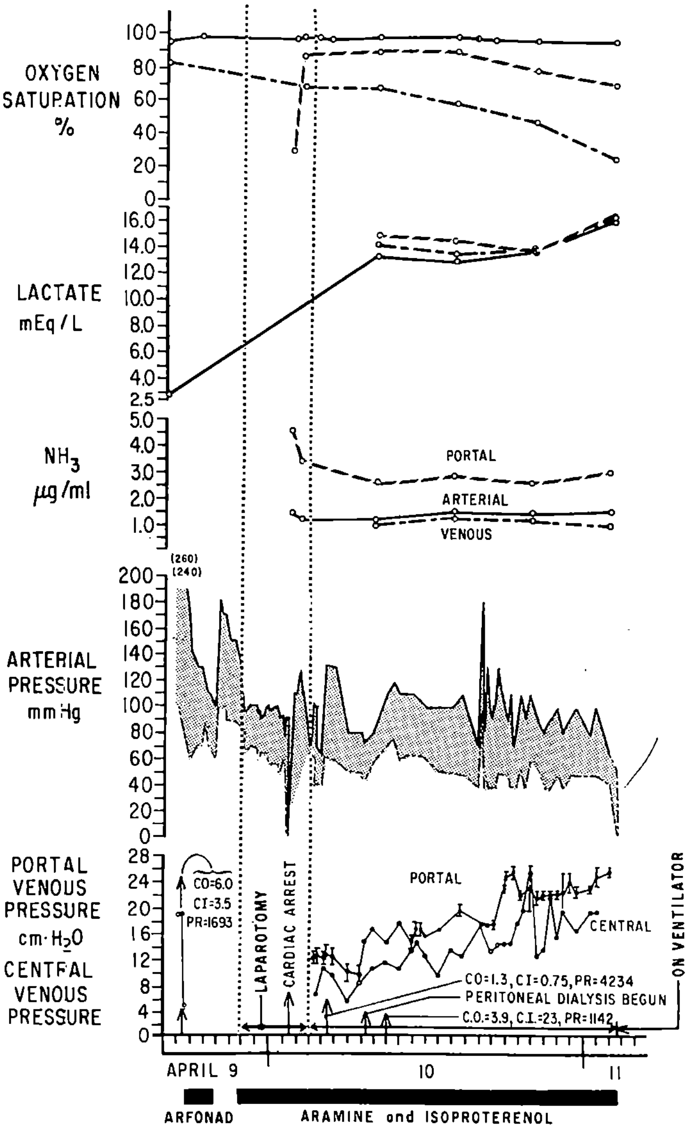


Fig. 8. M. D., a 57-year-old hypertensive female with acute aortic dissection causing occlusion of mesentric and iliac arteries. Shock and cardiac arrest developed during a laparotomy with fenestration procedure on the abdominal aorta and resection of ischemic colon. Patient expired 27 hours postoperatively in shock refractory to volume replacement, isoproterenol and metaraminol. The steadily rising CVP and low cardiac index (C.I.) suggest a cardiogenic element in the patient's shock. Note that all blood lactates were elevated but the curves did not diverge.

Smythe *et al.*[18] compared the oxygen content of arterial and portal venous blood in fasting patients in whom catheters had been inserted into the portal vein at laparotomy. They found the average arterial-portal venous oxygen content difference to be 1.9 ml/100 ml and concluded that, since so little oxygen was extracted by the gastrointestinal tract, "the portal venous blood must provide a substantial portion of the oxygen brought to the liver in man."

Bierman *et al.*[2] measured the oxygen content and saturation in portal venous blood obtained by percutaneous–transhepatic puncture in 11 patients with neoplastic disease and compared them with similar measurements from arterial and hepatic vein blood. Although portal venous oxygen saturation varied from 39.6% to 88.6% it was usually intermediate between hepatic venous and arterial values.

More consistent results were obtained by Storti and associates[19] who studied the portal and hepatic venous oxygen content and saturation in 5 normal subjects by means of umbilicoportal and hepatic vein catheterization. They noted mean values for oxygen content and saturation as follows: arterial, 15.62 ml/100 ml and 96.81%; portal venous, 13.44 ml/100 ml and 83.36%; and hepatic venous, 11.34 ml/100 ml and 64.41%. The arterial-portal oxygen content difference ranged from 1.87 to 2.89 ml/100 ml with a mean of 2.17 ml/100 ml. The portal-hepatic venous oxygen content difference ranged from 1.15 to 2.97 ml/100 ml (mean, 2.10 ml/100 ml).

White[22] measured portal venous blood gases by means of umbilical vein catheterization in seven resting patients, of whom two had normal livers, one hepatic metastases, and four cirrhosis. The portal venous PO_2 was in general midway between the arterial and the systemic venous values in the patients with normal livers as well as in the cirrhotics. The portal PCO_2 was more variable in this regard in both normals and abnormals. White's observation that administration of both phenylephrine and vasopressin caused a fall in portal PO_2 was confirmed by Piccone[14] and Viallet.[21]

Our studies confirm the high oxygen content of portal venous blood in fasting non-shocked patients. The mean values for portal venous oxygen saturation and for arterial-portal oxygen content difference in non-shocked patients are similar to those of Smythe *et al.*[18] and Storti *et al.*[19] Oxygen administration can increase the oxygen saturation of portal venous blood to 95–96%.

In the Shock Group the most noteworthy finding was portal venous oxygen desaturation, which was present to varying degrees in all five patients. The mean portal venous oxygen saturation was significantly lower, and the mean arterial-portal oxygen saturation difference significantly higher, in the shock patients than in the Non-shock Group.

Evidence for impaired splanchnic circulation or, more accurately, anaerobic metabolism in the gastrointestinal tract is provided by the differential elevation of portal blood lactate in three of the four fatal shock cases. The fourth patient did *not* show a widened portal venous pressure-central venous pressure gradient. White[22] found elevated portal lactates in patients who had portal hypertension and believed this indicated splanchnic circulatory stasis from portal venous obstruction.

The widening of the portal venous pressure-central venous pressure gradient in three of the five shock patients suggests impedance to flow of portal blood through the liver.[10] An obvious deficiency in the present study is the lack of measurement of hepatic venous blood levels and of hepatic arterial and portal blood flow. This is to form the basis of a future report. Experiments in hemorrhagic shock in the rat, a species which is similar to man in the anatomy of its hepatic veins, have demonstrated a progressive increase in hepatic resistance to portal blood flow in severe hypotension.[8,11] When arterial pressure declined to 30 mm Hg, clamping the hepatic artery did not affect hepatic blood flow, indicating that the portal vein was probably the only remaining source of blood flow. Tygstrup and co-workers[20] found that in man the portal vein provides the liver with approximately 50% of its oxygen requirement. A decrease in portal venous flow may well contribute to the centrizonal hypoxic necrosis which was a prominent autopsy finding in our shock patients.[4]

Kaplan *et al.*[12] suggested that the portal vein might be better termed an artery because of its kinetics and function. They found that the portal vein, the sinusoids, and the hepatic veins comprise a single hemodynamic unit, and claim that irrespective of hepatic arterial pressure or flow the sinusoids react only to portal pressure changes.

The ammonia studies show evidence of impaired liver function. In two of the severely shocked patients from the Shock-Trauma Recovery Group and in all three fatal cases from the Shock Group who had ammonia determinations, there was a significant accumulation of ammonia in the portal system. This has been noted in experimental hemorrhagic shock and attributed to increased ammonia production by intestinal organisms because of the intestinal stasis which occurs in the shocked state.[5] The concomitant elevations of ammonia in the arterial and central venous samples suggest the escape of ammonia through the liver into the systemic circulation. This phenomenon observed in canine hemorrhagic shock has been thought due to impaired hepatic urea-synthesizing mechanisms.[9] Hepatic dysfunction with or without centrizonal necrosis is almost certainly the result of hypoxia.

These findings if confirmed by further studies may have therapeutic implications. For example, glucagon increases hepatic blood flow in dogs by approximately 100%.[15] This increase is chiefly the result of increased portal venous flow and is secondary both to an increase in cardiac output and to splanchnic vasodilatation.[18] Its prophylactic value in avoiding the hepatic dysfunction which may complicate severe shock has yet to be elucidated.

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Ectopic Drainage of the Common Bile Duct

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Two patients are presented with ectopic drainage of the common bile duct, one entering the stomach and the second entering the first portion of the duodenum. They make the seventh patient with the common bile duct entering into the stomach and the 19 patients with anomalous drainage into the duodenum. The awareness of this and other biliary system anomalies is stressed to prevent damage to vital structures in this area. The theories explaining this anomalies are discussed.

ANOMALIES OF THE BILE DUCTS constitute a major hazard in patients undergoing biliary tract or gastric surgery. Gallbladder, bile ducts and arterial anomalies are very common. The usual pattern classically described in textbooks is seen in only 35% of the individuals. Operative injuries to the bile duct are frequently the result of the surgeon's lack of appreciation of the anomalies that can be encountered, aggravated by poor exposure and the compulsion to ligate the cystic duct before identifying the entire biliary system.

The purpose of this paper is to present two interesting patients with a rare anomaly of the biliary system who were treated at the University of Puerto Rico Hospital.

Case Report

B.T.R. (45-00-12). This is a 55-year-old white male patient admitted to the University Hospital on July 31, 1970, with obstructive jaundice. He had a cholecystectomy done on August 9, 1968 at another hospital after two months of intermittent jaundice. The common duct was found to enter into the lesser curvature of the stomach, about 6 cms above the pylorus (Fig. 1). Operative cholangiogram showed dye entering the stomach. Exploration of the common bile duct was performed and a few stones were recovered. No operative T-tube cholangiogram was done. Biopsy from the abnormal duct was reported as common bile duct wall with fibrosis. A T-tube cholangiogram done on August 19, 1968, revealed no passage of dye into the gastrointestinal tract for which a second operation was performed on August 26, 1968. Operative cholangiogram showed stones and no passage of dye into the stomach. Three stones were removed and a T-tube again left in the common bile duct. Repeated T-tube cholangiograms done on September 2, 1968, and on January 15, 1969, revealed stones, but for unknown reasons the T-tube was removed on April 1970 and three months later he developed jaundice (July 1970) accompanied by right upper quadrant pain for which he was admitted to our hospital. The patient denied loss of weight, fever or chills. Past history, family history and review of systems were noncontributory. Physical examination revealed normal vital signs. The sclera was icteric. The abdominal examination disclosed a well healed right subcostal scar and moderate right upper quadrant tenderness. Laboratory findings revealed serum amylase of 172 units, prothrombin time normal, alkaline phosphatase 170 international units (Normal 30–85); bilirubin, 2.4 mg%, direct 1.2; normal serum proteins. EKG and chest X-rays were normal. Upper gastrointestinal X-rays showed normal stomach and duodenum; reflux into the esophagus was observed but no hiatal hernia was seen. Gastroscopy revealed a normal antrum and pylorus; the mucosa of the body and fundus was normal. There was a yellowish material with bubbles in the lesser curvature of the stomach at its mid portion but no orifice could be identified.

On August 12, 1970, the patient was explored through a right paramedian incision. The adhesions from the previous operation were divided. The common bile duct was markedly dilated, measuring 3.5 cm with thick walls and draining into the lesser curvature of the stomach. The hepatic ducts were also dilated. Few stones were felt in the common duct. Operative cholangiogram showed distal partial obstruction, but with some dye entering the stomach (Fig. 2). The duct was opened and three large stones were removed; the hepatic ducts were irrigated with saline. A probe was inserted into the distal common duct but the instrument could not be advanced into the stomach. A T-tube was placed and repeat T-tube cholangiogram revealed distal obstruction at the entrance of the common duct into the stomach and again some dye in the stomach. The duct was divided and a choledoduodenostomy constructed in a single layer without internal splinting. The patient had a good postoperative course and was discharged on

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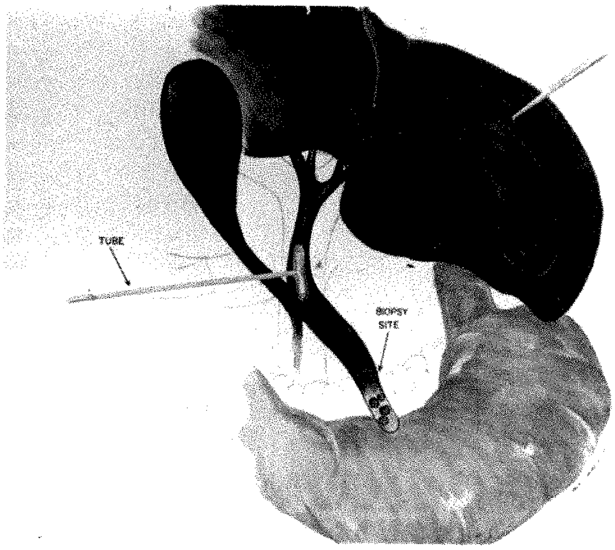

FIG. 1. Artist's representation of the common bile duct entering into the lesser curvature of the stomach.

August 21, 1970, nine days after the operation. He had remained asymptomatic. An upper gactrointestinal series on May 15, 1972, showed the choledochoduodenostomy widely open.

J.D.M. (45-86-41). This is a 59-year-old male patient admitted to the University of Puerto Rico Hospital on September 8, 1970, with carcinoma of the lesser curvature of the stomach. Physical examination was unremarkable. Laboratory work-up revealed alkaline phosphatase of 180 units. Transaminases, bilirubin, prothrombin time, urea nitrogen and electrolytes were normal. Chest X-rays and EKG were also normal, as well as liver scanning. At exploration on September 25, 1970, a huge carcinoma of the stomach attached to the pancreas was found. The common duct was dilated (3 cm) and apparently entered into the distal stomach. The gallbladder was elongated in a horeshoe shape and no stones were felt. A total radical gastrectomy with splenectomy and distal pancreatectomy was done. Continuity of the gastrointestinal tract was re-established by doing an esophagojejunostomy and jejunojejunostomy. Operative cholangiogram showed passage of dye into the duodenum. There were multiple diverticuli in the first portion of the duodenum. The common duct was opened and a probe inserted distally but failed to pass into the gastrointestinal tract. The papilla of Vater was visualized by injecting saline through a T-tube in the common duct, draining 1 cm distal to the pylorus. Biopsies proximal and distal to the entrance of the papilla of Vater showed duodenal mucosa. T-tube cholangiogram demonstrated a large, capacious gallbladder and common duct (Fig. 3). No demonstrable stones obstructed the common duct. There was passage of dye into the duodenum.

The patient had a good postoperative course and was discharged on October 8, 1970. Pathologic examination of the specimen revealed adenocarcinoma of the stomach with penetration into the pancreas and metastasis to 2 out of 34 lymph nodes. The proximal and distal lines of resection were free of tumor.

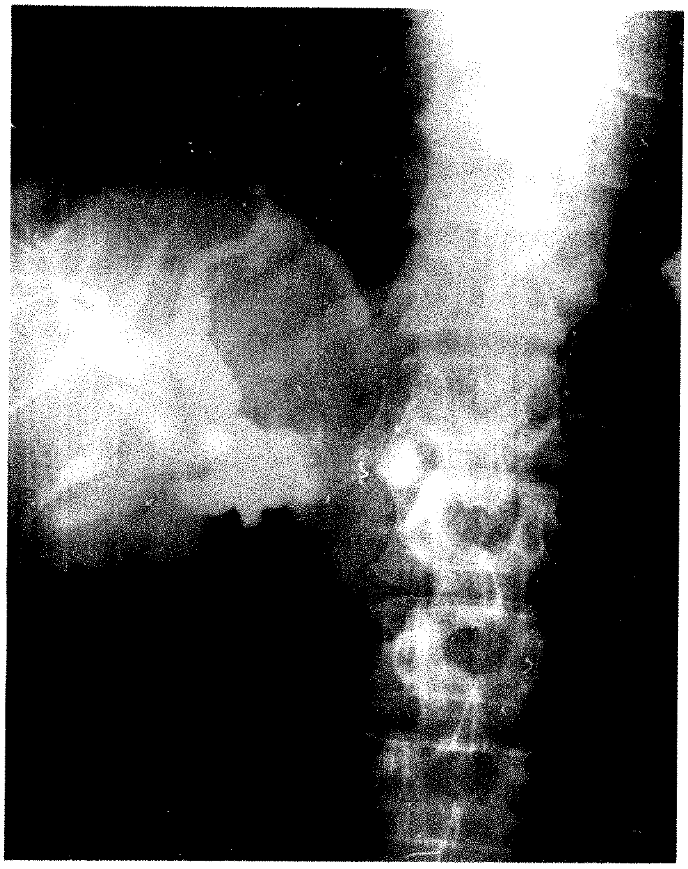

FIG. 2. Operative cholangiogram showing partial obstruction, but some dye in the stomach (upper right corner).

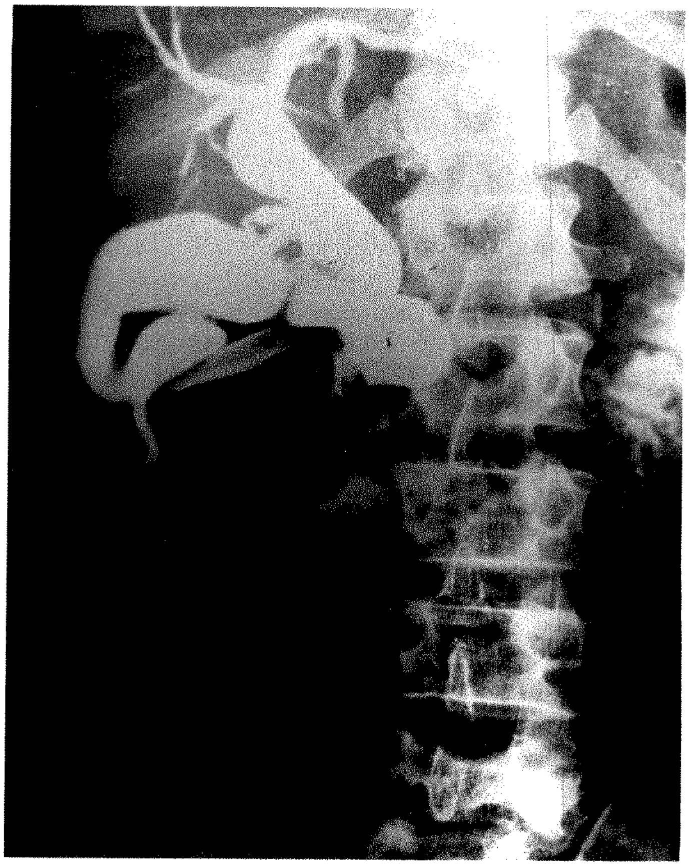

FIG. 3. Large capacious gallbladder and dilated common bile duct.

Comments

It has been estimated that about 90% of all bile duct strictures are caused by errors in surgical technique, due to inadequate knowledge of the structures at the hepatic pedicle. Variation in the arteries are more frequent than those of the bile duct. Multiple anomalies of the biliary system have been described including anomalies of number, form, size and position of the gallbladder, accessory hepatic ducts, anomalies of the cystic duct and of the hepatic and cystic arteries.[8,10,15]

It has been demonstrated that only after thorough dissection of the gallbladder pedicle can the surgeon be sure of not doing any harm.[6,12]

Anomalies of the biliary tract are so common and variable that no surgeon who operates upon the gallbladder and bile ducts can afford to ignore their existence. Some anomalies of the biliary system are relatively common, while others are unusually rare.[5,9]

In 1970 within a period of two months we had the rare opportunity of operating upon two patients with an anomalous insertion of the common duct, draining into the antrum in the first patient and into the first portion of the duodenum on the second patient.

Drainage of the common bile duct at sites other than the second portion of the duodenum is an anatomical curiosity. The rarity of this finding is indicated by the infrequent publications on this respect; only sporadic cases have been reported in the last thirty years.

Probably the first authentic[2] report in the older literature (Fig. 4) was made by Vesalius in 1543 who described a patient with two ducts; one entering into the stomach antrum, and the lower one entering into the duodenum. Similarly Courvoisier mentioned another case attributed to Graseccius in 1605 in which one duct drained into the duodenum and another into the pylorus. In the nineteenth century two other cases were described, that of Bleifus in 1839, in which the common duct entered the stomach but the exact place was not mentioned and the other case was from Laennec in which the common bile duct entered into the lesser curvature of the stomach just below the cardia.[13]

In the more recent literature, Filippini in 1931, (Fig. 5) described a patient with jaundice and no stones in which the common bile duct entered into the pylorus and the pancreatic duct was 11 cm below the insertion of the choledochus. Everett and Macumber[4] in 1942, described a patient similar to that of Vesalius, with one duct entering the stomach and another duct entering the duodenum, but the gallbladder and cystic duct were absent.

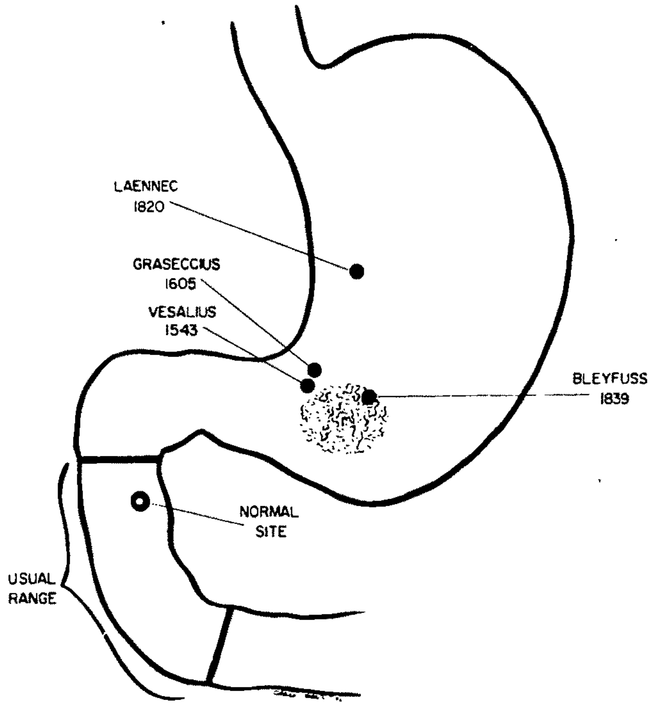

FIG. 4. Sites of ectopic drainage of common bile duct into th stomach (before 1900).

In regard to the insertion of the common bile duct in the first portion of the duodenum, seven cases were described in the older literature[2]. Two cases (Fig. 6) were ascribed to Fallopius (1606) as described by Courvoisier. Diemerbroek described the third case in 165 in a patient with two ducts entering into the duodenu a finger breadth apart. Blasius, in 1674 and 1677, described three patients; two with separate entrance o the pancreatic and common bile ducts into the duodenum, the other with a divided Y shaped commo duct both entering the duodenum. The last case wa ascribed to Vater in 1748. In the modern literature ther are 11 more cases reported (Fig. 7). The first case wa reported in 1803 by Vetter. In 1931, Rodríguez an Adriano described a patient with an accessory bile duc entering separately from the common bile duct 1.5 m apart. Kehr, in 1906 and 1912, described two patient and Karpa in 1906 and Katz in 1930 described tw patients with splitting of the common bile duct wit congenital atresia of the duodenum, one duct enterin above and the other below the area of atresia.

Gentile,[7] in 1931, presented a case with a commo duct entering in the normal position and an accessor duct entering 3 cm above the normal duct with proxima and distal connections between the two ducts. Th entrance of the common duct was occluded.

In 1933, Boyden[2] reported a patient with double ductu choledochus, the upper entering the first portion of th duodenum. He mentions that where there are tw ducts present, one exhibits the tendency to becom occluded or to undergo complete atrophy.

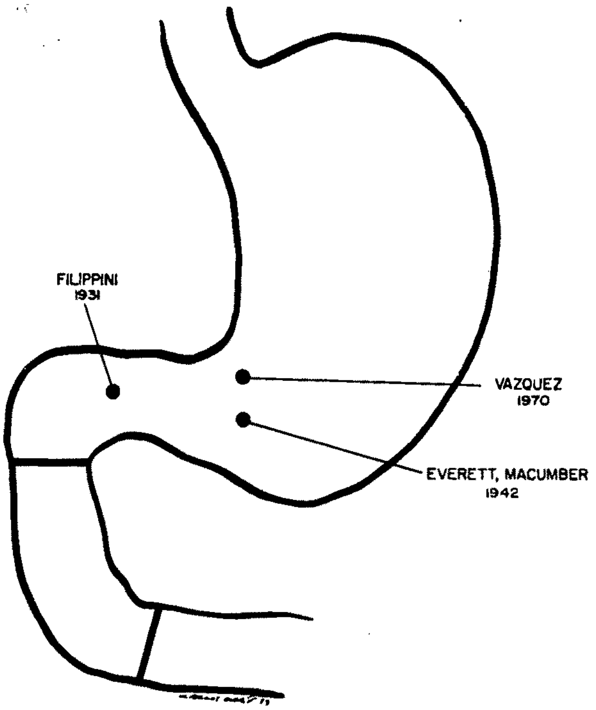

FIG. 5. Sites of ectopic drainage of common bile duct into the stomach (after 1900).

In 1935, Swartley and Weeder[17] reported a patient with choledochal cyst and double common duct, both entering the duodenum. Francis D. Moore *et al*,[16] in 1963, published a case report in which the choledochus and pancreatic duct drained into the first portion of the duodenum. This patient died as a result of transection of the ductus following gastrectomy for upper gastrointestinal bleeding.

Insertion of the common bile duct into the third portion of the duodenum has also been described. Wood,[19] in 1966, described the 20th case and made reference to the previously presented cases including 16 ascribed to Lurje in 1937,[14] in autopsy specimens.

Embryology of the Biliary Tree

The liver originates from the hepatic diverticulum, arising from the ventral aspect of the gut at the junction of the foregut and the midgut. A transverse furrow divides the hepatic diverticulum into a cephalic portion and a caudal portion; known as pars hepatica and pars cystic, respectively. The pars hepatica gives rise to the liver and hepatic and common hepatic ducts. The pars cystica gives rise to the gallbladder and the cystic duct. The common bile duct is derived from the hepatic antrum which is the common portion of the original hepatic diverticulum. Cords of cells from the pars hepatica grow into the septum transversum giving rise to the hepatic parenchyma and bile canaliculi. The pars cystica is solid and later by resolution of its epithelial contents becomes hollow.[8,9,11]

Embryological Explanation

Boyden,[2] in an excellent article divides the ectopic common bile ducts into two groups: A, those bordering upon the pylorus or draining higher into the stomach; and B, those situated on the duodenum within 3 cm of the usual site of the ampulla of Vater. He proposes three different explanations:

1. That the ectopic duct (ductus hepato-entericus) is an atavistic structure representing a throw-back to the double hepatic outgrowths found in reptiles, birds and some fishes.
2. That it is merely a supernumerary outgrowth, analogous to an accessory pancreas.
3. That it is due to a chance subdivision of the primary hepatic furrow of the embryo, resulting from some rare disturbance in factors that control the initial phase of development of the biliary system.

Objections to the first theory are that if this were an atavistic condition it should be more frequent in other mammals. Boyden[1] reports having examined 10,000 livers (2,500 cats, 2,500 calves, 2,500 pigs and 2,500 lambs) without finding a single case of double choledochus. The objection to the second theory is that no independent masses of hepatic tissue emptying into the gut have ever been reported. Therefore, the third explanation is

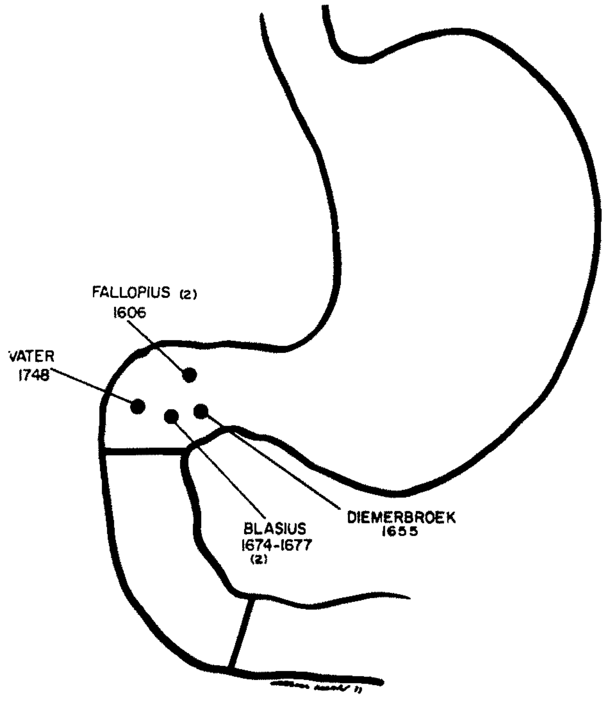

FIG. 6. Common bile duct entering ectopically into the duodenum (older literature).

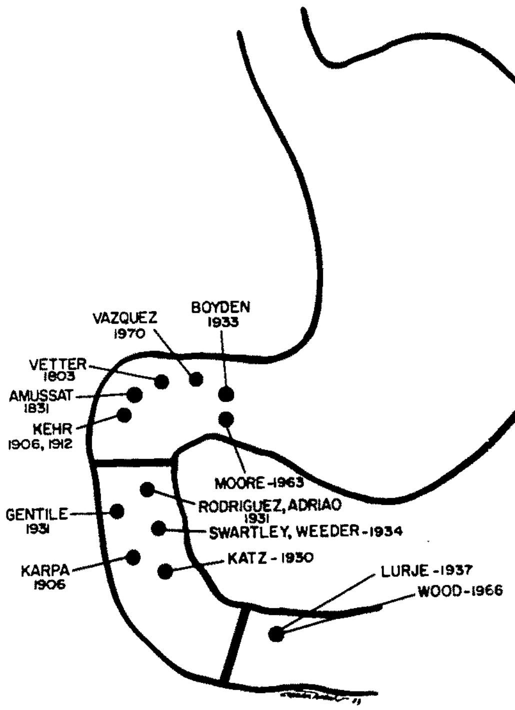

FIG. 7. Common bile duct entering ectopically into the duodenum (modern literature).

the only one left to elucidate these anomalies. All cases are interpreted on the basis of chance elongation and early subdivision of the primitive hepatic furrow into two divisions, corresponding to pars hepatica and pars cystica. If subdivision occurs very early leaving the pars hepatica above the zone of growth that separates stomach from duodenum, then the pars hepatica will develop into a duct emptying into the region of the pylorus. If the division occurs below this zone of growth with the upper diverticulum bordering upon the stomach, then both ducts will empty into the duodenum, but at varying distances from each other. If separation occurs when the furrow is approaching its definitive position, then the two ducts will empty into the duodenum side by side. Experimentally it has been demonstrated by Wolff[18] that the liver could have a double origin. The two primordia originate from the lateral ends of the endoderm giving rise to the digestive tube. When the digestive tube is not closed rapidly enough the two primordia develop separately.

In patients having only one duct entering into the first portion of the duodenum, we must assume that obliteration of the other duct occurs during fetal life. Our two patients have ectopic insertion of the common bile duct, nevertheless, we do not know how the pancreatic duct drains. Since they were not visualized, we assume that they drain by different opening. We must postulate that the hepatic and pancreatic primordia developed independently.

Acknowledgments

We are indebted to Dr. Josel Szepsenwol for his assistance in the embryological explanation and to Dr. Donald Graber for referring us the first patient.

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Serum Antibody in Patients with Breast Disease:

Correlation with Histopathology

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Antibody to a breast cancer antigen was detected by immunodiffusion or complement fixation in at least one serum sample in 46% of 84 patients with a diagnosis of carcinoma, 34% of 96 patients with fibrocystic disease and 25% of 44 patients with fibroadenoma. A single serum sample obtained from screenees of the Detection Center for Breast Diseases was tested by immunodiffusion only and antibody was found in 3 of 206 screenees (1.5%). Eleven of 13 patients with breast cancer metastatic to lymph nodes and no detectable serum antibody either had recurrence or were dead within 12 months of mastectomy. Fifteen of 18 patients with breast cancer metastatic to lymph nodes and with detectable serum antibody were alive and free of disease for up to 24 months. Histologic slides from patients with a diagnosis of fibrocystic disease or fibroadenoma were reviewed for the presence of ductal epithelial hyperplasia. Ductal epithelial hyperplasia was present in a similar per cent of patients with no detectable serum antibody as those with antibody detected in the serum. Severe sinus histiocytosis of the axillary lymph nodes was present in 45% of those cancer patients with serum antibody and only 11% of those cancer patients with no detectable serum antibody.

SERODIAGNOSIS OF DISEASE began when Widal,[14] in 1896, reported that the sera of patients suffering from typhoid fever agglutinated a suspension of typhoid bacilli. In 1906, Wasserman, Neisser and Bruck[12] described a complement fixation test for syphilis. They utilized the extract of syphilitic lesions from man and monkey as a source of antigen. Ironically, they believed that the antigens of *Treponema pallidum* present in the extracts react with antibody to this organism and hence fix complement. One year later, Landsteiner, Muller and Potzel[7] reported that alcoholic extracts of normal guinea pig organs fix complement when reacted with leutic sera. These reminders of the early history of the serodiagnosis of syphilis are helpful in the early history of searching for a serologic means of detecting cancer.

In recent years, the work from Gold's laboratory[10] on carcinoembryonic antigen has stimulated great interest in the serodiagnosis of cancer. Although the utilization of CEA test for the early detection of cancer seems less hopeful from recent data, the entire spectrum of serodiagnosis of cancer has been broadened.

In our preliminary report,[5] we noted the presence of ductal epithelial hyperplasia in three patients with serum antibody. Hence, in this communication we wish to compare the incidence of serum antibody in patients

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with breast disease with serum antibody in screenees from the Detection Center for Breast Diseases.

Methods

Source of Sera

Sera were obtained from patients with breast disease under the protocol of the Kansas Breast Study.[6] The sera were obtained from women with a breast mass preoperatively, and approximately one and four weeks after breast biopsy or mastectomy. These sera were sent to the laboratory at KUMC for testing. Single serum samples were obtained from 54 volunteers without breast disease. In addition, a single serum sample was obtained from 206 women screenees of the KUMC Detection Center for Breast Diseases.

Source of Antigen

Breast cancer tissue from a primary lesion, as well as from a liver replaced by metastatic breast cancer, was used to prepare a breast cancer antigen (BCA) described below.

Antigen Preparation

BCA was prepared in a manner previously described.[2] In brief, the breast carcinoma tissue was homogenized in a Sorvall Omnimixer and subjected to a series of differential centrifugations to obtain cell sap, which was concentrated by ultrafiltration to one-half the original tumor volume. This concentrated cell sap was designated "BCA" and was used for immunodiffusion and immunoelectrophoretic analyses.

To provide material suitable for complement fixation studies, BCA was fractionated on Sephadex G-200 (85 × 5 cm column), using phosphate buffered saline (PBS), pH 7.2, as the eluant. Pool #1 was concentrated by Diaflo ultrafiltration (PM-10 membrane) to the original sample volume applied to the column and used in complement fixation.

Immunodiffusion

Immunodiffusion analyses were performed according to Ouchterlony[8], using 1.0% agarose in PBS. Plates were incubated at 4 C. Lines of precipitation appeared after one to two days of incubation.

Complement Fixation

The complement fixation test was performed as previously described[2] according to a modification of the technique of Wasserman and Levine.[13] Complement, antiserum and antigen controls were included in every test. The reported titers are the highest serum dilutions which gave greater than 10% complement fixation with no anticomplementary effect in the serum control. Hence, in sera with anticomplementary effect, the first dilution failing to show anticomplementary effect was used for final testing (eg. 1:80, 1:160, etc.).

Absorbed sera

For determination of the presence of heterophile antibody as the serum antibody reacting with BCA, serum demonstrating reactivity to BCA in immunodiffusion were absorbed as follows:

Erythrocytes. Separate 0.5 ml aliquots of each positive sera were incubated with 0.5 ml of washed and packed erythrocytes of sheep, rabbit and bovine origin. The serum-erythrocyte suspension was incubated at 37 C for 30 minutes, centrifuged, and the absorptions repeated a second time before testing.

Guinea-pig Tissue. 0.5 ml aliquots of each positive serum were incubated at 37 C for 30 minutes with 1.0 ml of washed and packed guinea pig kidney tissue which had been minced and then homogenized in phosphate buffered saline, using a Sorvall omnimixer.

Histopathology

Histologic slides from 39 patients whose breast masses were diagnosed as fibrocystic disease or fibroadenoma were reviewed for the presence of ductal epithelial hyperplasia. In addition, slides from 29 breast cancer patients were scruitinized for lymphocytic infiltration as well as for lymph node hyperplasia.

Results

Serum from 226 patients undergoing breast biopsy and/or mastectomy were examined by the two tests described above. At least two serum samples were available from 84 patients with carcinoma of the breast, 96 patients with fibrocystic disease and 44 patients with fibroadenoma. In many, the busy practicing physician failed to obtain either the second or third sample. If both the second or third samples were not sent for testing, the initial serum sample was not tested.

Antibody to BCA was found in 25% and 34% of sera from patients with fibroadenoma and fibrocystic disease respectively. Antibody was found in 46% of sera from patients with carcinoma. Comparison of detection of antibody by each test, immunodiffusion and/or complement fixation, can be seen in Table 1. As expected complement fixation proved more sensitive in detecting

TABLE 1. Antibody in Sera of Patients with Breast Disease

Diagnosis	No. Patients	Antibody Detected I.D.	C.F.	Both	NEG.	Total + (%)
Carcinoma	82	9	25	5	45	39 (46%)
Fibrocystic Disease	96	4	25	4	63	33 (34%)
Fibroadenoma	44	4	5	2	33	11 (25%)

antibody. Good concordance was not seen from results of the two tests and has been presented previously.[2] While discordant results obtained from testing some sera undoubtedly is due to the fact that many sera were anticomplementary, other data suggest that the presence of more than one antigen may account for different results.

In a previous report,[2] reactivity of these sera with a "normal breast antigen" prepared from virginial hypertrophy tissue and with "diseased breast antigen" prepared from a breast with severe fibrocystic disease has been compared.

Serum from 54 volunteers (44 females and 10 males) without breast disease were tested for antibody to BCA by immunodiffusion and gave negative results. These patients included prepartum and postpartum volunteers, healthy males, women with non-breast cancers, as well as some volunteers with chronic systemic diseases other than cancer.

The Detection Center for Breast Diseases at the University of Kansas Medical Center opened September, 1973. In addition to history and physical examination, mammography and thermography, a blood sample is obtained from each screenee. Using immunodiffusion only, 206 sera have been tested for antibody to BCA. Five sera were positive; two patients were postoperative for cancer of the breast and melanoma and the remaining three failed to give a history for a cancer operation and were judged by screening methods not to have breast cancer at this time. However, two of these screenees had abnormal mammograms; one was noted to have "benign" calcifications and one was noted to have "benign masses." The third screenee had no abnormal findings. Data from Table 2 illustrate comparative data from immunodiffusion tests on the frequency of positive sera from patients with carcinoma, fibrocystic disease or fibroadenoma. In comparison with any single sample, the striking increase in frequency of antibody in the third sample of cancer patients should be noted.

Studies on the specificity of antibody and comparison of antigenicity of different breast cancer tissue are now underway. Preliminary data brings forth evidence that the antibody reacts with similar antigen preparations from other cancers. Of 12 cancer patients with antibody reactive with BCA in immunodiffusion, seven reacted with ovary and colon carcinoma. In addition, six of these seven sera reacted with sarcoma, and two with melanoma. Three of the 12 positive sera from patients with fibrocystic disease reacted with antigen preparations from other cancers; one reacted with ovary, colon and sarcoma, one reacted with only ovary and the third reacted with melanoma and sarcoma. Two of the five positive sera from patients with fibroadenomas formed a line of precipitation with antigens from other cancers; one reacted with only ovary and melanoma.

Studies to determine the nature of the antibody reacting with BCA yielded interesting, if not unexpected, results. Aliquots of 13 positive sera were absorbed with rabbit, sheep and bovine erythrocytes, and 11 sera with guinea pig kidney tissue. Reactivity with BCA was not removed in any sera by absorption with bovine erythrocytes and by rabbit erythrocytes in only one sera. Interestingly, in three sera, sheep erythrocytes and in four sera, guinea pig kidney tissue each removed reactivity with BCA.

The biological significance of the antibody detected is being investigated by comparing its presence or absence with status of the regional lymph nodes and survival of the patients. All patients without axillary lymph node metastases, regardless of the presence or absence of serum antibody to BCA, do not have recurrence at this early date. On the other hand, of 13 patients with metastases to axillary lymph nodes and no detectable antibody to BCA, 11 are either dead or have recurrence within one year. The other two patients had radical mastectomy less than six months ago. In contrast, of the 18 patients with metastases to axillary lymph nodes and sera positive for antibody to BCA, 15 are alive without evidence of recurrence; many are over one year since mastectomy. These data pertain only to patients who were judged to have a "curative" procedure at the time of surgery.

Sections from 39 patients with fibrocystic disease or fibroadenoma were evaluated for ductal epithelial hyperplasia; a similar incidence was found in patients with antibody and with no detectable serum antibody (Table 3).

Suggestive evidence that a correlation exists between lymphocytic infiltration of the primary lesion and the presence of serum antibody was found by reviewing

TABLE 2. *Preciptitating Antibody in Sera of Volunteers for Kansas Breast Study and the Detection Center for Breast Diseases*

	Serum Sample											
		#1			#2			#3			Total	
Patients	No.	Pos.	%	No.	Pos.	%	No.	Pos.	%	No.	Pos.	%
Carcinoma	84	6	7%	51	7	14%	44	9	20%	84	14	17%
Fibrocystic Disease	96	7	7%	56	2	3.6%	52	2	4%	96	8	8%
Fibroadenoma	44	3	7%	28	1	3.5%	31	2	6.5%	44	6	14%
Screenees DCBD	206	3	1.5%									

sections of 28 patients with carcinoma. Furthermore, a strong correlation exists between sinus histiocytosis in the axillary lymph nodes of these patients and the presence of serum antibody (Table 4).

Discussion

In a preliminary study,[5] antibody was found in the serum of two patients with carcinoma of the breast and one patient with severe fibrocystic disease. Since these results raised the speculation that determination of the presence or absence of this antibody might aid in early detection or prognostication following therapy, the Kansas Breast Study was initiated to obtain sera from a large number of patients undergoing breast biopsy or biopsy followed by mastectomy. This study is carrried out with the assistance of physicians throughout the state of Kansas. Serum samples are obtained before surgery, at the time of suture removal, and at the one month followup visit. Using immunodiffusion and complement fixation tests, antibody reactive with a breast cancer antigen was found in 46% of 84 patients with the diagnosis of carcinoma of the breast. This low percent of positivity raised the question of the value of this test in early detection of breast cancer. However, since all of these patients already had a breast mass, this question could not be answered. The failure to detect antibody in 54% of carcinoma patients may be due to a lack of antigen(s) in the carcinoma of those patients similar to antigen(s) in the test reagent. Serum obtained from screenees of the Detection Center for Breast Diseases should bring forth data to resolve this problem. Interestingly, serum from the one patient with carcinoma, out of the first 206 screenees, failed to react with BCA. Histologic studies failed to reveal any correlation between tumor type and the presence of serum antibody. Another explanation might be that following radical mastectomy, sufficient tumor antigen remained to absorb antibody from the circulation and render antibody undetectable by test methods utilized. The early clinical course of patients with positive axillary lymph nodes would support this explanation for at least some of the 54% with undetectable serum antibody; eg. 11 of 13 patients with positive axillary lymph nodes and no antibody had recurrence within one year. In contrast, only three of eighteen patients with positive axillary lymph nodes and antibody have recurrence of their cancer from one to two years postoperatively.

Interestingly, this raises the possibility that the presence of antibody postoperatively may be utilized for seroprognosis. Supporting data came from the positive correlation of lymphocytic infiltration in the tumor in patients with antibody and confirms other reports which have related lymphocytic infiltration with a more favorable clinical course.

TABLE 3. *Relationship of Serum Antibody to Histopathology of Breast Tissue*

Diagnosis	Serum Antibody	No. Pts.	Moderate to Severe Ductal Epithelial Hyperplasia	Severe Ductal Epithelial Hyperplasia
Fibrocystic Disease	+	12	12	9
Fibroadenoma	+	8	8	5
Fibrocystic Disease	−	8	8	7
Fibroadenoma	−	11	11	8

The finding of serum antibody in patients with diagnosis of the biopsy specimen as "fibroadenoma" or "fibrocystic" disease raised the question of the value of this finding in early diagnosis and the entire problem of specificity. On the other hand, the finding of antibody in only 1.5% of 206 screenees from the Detection Center for Breast Diseases suggests that this crude test is leading in the proper direction. Data showing cross-reactivity with antigen preparations from other cancers further illustrates a central problem in the test system at this time, the lack of a mono-specific and standard antigen preparation. Hence, while the test for CEA has problems incumbent in the use of a heterologous system, the test system utilizes a standard test reagent, a heterologous antiserum. In the present stage of development, of necessity, we have used a test reagent, antigen preparation from breast cancer tissue, which may vary in antigens as well as strength of antigenicity. In fact, early studies comparing reactivity of antigen preparations from different sources support this thesis. Studies are underway to ascertain the reactivity of antigen preparation from breast cancer tissue obtained from several patients as well as primary and/or secondary lesions. These results will be compared with different methods of antigen preparation as well.

At the same time, several investigations of the serum antibody are in progress. The cross-reactivity with other cancers was noted above, and previous data has shown some cross-reactivity with tissue of the virginal hypertrophy type. Presently, breast tissue from a 17-year-old accident victim is being treated as "normal" control tissue. Rapaport[9] has described the occurrence of hetero-

TABLE 4. *Relationship of Sinus Histiocytosis of Axillary Lymph Nodes and Lymphocytic Infiltration of Tumors to Serum Antibody in Patients with Carcinoma of the Breast*

Antibody	Lymph Node Sinus Histiocytosis			Lymphocyte Infiltration of Tumor		
	Mild	Moderate	Marked	Mild	Moderate	Marked
Positive	2*	9	9	5	10	4
Negative	4	4	1†	4	4	1

* 1 had total replacement of all nodes by tumor.
† Male.

phile antibody in transplantation patients. While 10 sera tested in the present study had agglutinins to many species' erythrocytes as described for the normal population, the reactivity to BCA was removed completely from three of 13 sera by absorption with sheep erythrocytes, and from four of 11 sera by absorption with guinea pig kidney tissue.

The report of Tönder[11] described an immunoglobulin Fc receptor on human tumors raised the possibility that a similar mechanism might be involved in our test system. Since pepsin digestion did not destroy reactivity of the two positive sera, this explanation does not seem likely.

With earlier data showing a strong correlation between severe large duct epithelial hyperplasia and carcinoma of the breast,[4] early studies of histologic sections from patients with fibrocystic disease or fibroadenoma were correlated with the presence or absence of serum antibody to BCA. Unexpectedly, we found that a similar percent of patients with serum antibody and patients with no detectable antibody had ductal epithelial hyperplasia. Therefore, one might speculate that the antibody is not formed as an immune response to the hyperplasia. Certainly, hyperplasia and antibody may be unrelated effects of the oncogenic agent.

Review of histologic sections of the primary breast cancers and axillary lymph nodes showed a correlation of serum antibody to both lymphocytic infiltration of the primary lesion and sinus histiocytosis of the axillary lymph nodes. Black and Asire[1] have reported a correlation of these histologic changes with patient survival. While only indirect, our data further suggests that antibody to BCA may be of biological significance. For years, clinicians have tended to impute biologic activity of tumors on morphologic data. Lest the preliminary data presented herein be construed to impute biologic significance to the serum antibody found reactive with BCA, the central problem in these studies of no standard test reagent must be reiterated.

Acknowledgments

The cooperation and participation of many physicians in the State of Kansas has been an exciting feature of this study. The technical assistance of Mrs. Carol Boettcher, Mrs. Helen Finlen Mrs. Asineth Hartman, Mrs. Peggy Jenkins and Mrs. Paul Morse is greatly appreciated.

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Discussion

Dr. Warren H. Cole (Asheville, North Carolina): You realize that the immunology, particularly therapeutic, in cancer is a brand new procedure, only four or five years old, and Dr. Humphrey is truly a pioneer in this field. You will recall that he reported antibody found in 40 or 42% of patients with cancer of the breast, and in 32% of patients with fibrocystic disease, and in 25% of patients with fibroadenoma, but none—or perhaps 1.5%—in 50 normal individuals.

Now, I consider the latter point more important than the others, because it indicates a certain degree of specificity. But the presence of an antibody in 27% of patients with fibrocystic disease and 32% of patients with fibroadenoma appears disconcerting.

Dr. Humphrey states in his paper that this may be because there is not sufficient specificity in the antibody, and he's trying to make them more specific; but that point does not disturb me too much. You may recall the classical experiments of Jim Grace from Roswell Park several years ago, showing that when extracts from the breasts of normal people were injected into newborn mice, they yielded an incidence of maglignancy—malignant disease —in the adult mice in a very low per cent, no greater than the per cent in the controls. But the extracts of benign tumors yielded a per cent of malignant disease in the mice just as great as the extracts of the malignant disease.

This indicates that there may be some relationship between benign disease and malignant disease which we don't yet understand.

Another part of Dr. Humphrey's data appears to be very important to me; namely, that 57% of breast cancer patients with negative axillary nodes had a serum antibody, whereas only 20% of patients with positive nodes had antibody. This indicates that the patients with negative nodes have more protection than the ones with positive nodes. And you might say: Well, we already know that. But the addition to our knowledge may be in the supposition that, regardless of the status of the nodes, the patient with positive antibody will have a better prognosis; and I think that that was one of Dr. Humphrey's last remarks, that he was putting a lot of blue chips on that point.

We hope that this early start to discover an antibody may lead to the day when we can stimulate the antibody formation to the point of cure of the patient, and the stimulation by BCG may improve the antibody reaction. And I'd like to ask Dr. Humphrey that question: Has he used any BCG in trying to stimulate antibody production?

The big priority in the possibility of immunologic cure is the ability of the patient to form antibody. We have known for 10 or 15 years that animals could form antibody, but this is one of the first demonstrations that human beings can do so.

Some of us just came from a meeting of the American Cancer Society Conference on Virology and Immunology in New York, just two or three days ago. You know, of course, that 15 or 20 years ago none of our ivory tower friends thought that tumors were antigenic, or even would produce antibodies. There was a greater percentage of believers in the immunology of cancer among the ivory tower people there in New York than there was 10 years ago by far, but there were still two or three of our ivory tower friends who very emphatically stated that vaccines were not possible in human beings.

But I'm quite sure they're wrong, and most of the individuals at that meeting thought they were wrong too. But, in summary, I do believe that this represents a very optimistic future for the subject of immunology in cancer, and we hope that in the years to come we can get some successful results from it.

Dr. Benjamin F. Byrd, Jr. (Nashville): Certainly, it's from this direction that our next major improvement in the management of breast cancer must come. The presence of host resistance to breast cancer has been for years a clearly recognized fact to the clinician, who has seen spontaneous remissions, apparent spontaneous cures, who has seen lymph nodes recede following the removal of a primary tumor, or the extremely slow progression of late and distant metastases.

Unfortunately, too much of our experience has been of a negative type: the sudden development of an almost explosive rapidity of growth of a long-standing breast lump, or the development of sudden, late recurrence with a rapid progression to death of the breast cancer patient.

The identification of clinical evidences of the immune response by serologic diagnosis could be added to our present ability to evaluate sinus histiocytosis and the lymphocytic infiltration which is occasionally seen in slowly progressing breast carcinomata.

The work of Kim and his group from Roswell Park lends considerable weight to Dr. Humphrey's efforts toward serologic evaluation of patients with breast cancer. Kim has been able to convert the nonmetastasizing breast cancer found in animal models into a type of carcinoma which metastasizes to lymph nodes and viscera. This conversion has apparently been accomplished by stripping a capsule from the cancer cells themselves. The material in this capsule has produced a response identifiable with some of the fractions of the carcinoembryonic antigen.

While I would like to propose many questions to Dr. Humphrey, I will ask only three. First, how does this study relate to inflammatory carcinoma of the breast? Second, are there differences in the histologic appearances of the breast carcinoma which relate to responses to his breast cancer antigen? And third, has he any comment on the apparent origin of the lymphocytes which are found especially in the medullary carcinomas of the breast?

Chairman Zeppa: Dr. Humphrey, before you close, would you consider answering one more question? And that is, have you had an opportunity to look at the antibody in patients with plasma cell mastitis of the breast, or with fat necrosis of the breast, simulating a tumor?

Dr. Loren J. Humphrey (Closing discussion): I'm sorry, we have not had any patients with either of those, but if someone in the audience has such a patient, send us a couple of blood samples. That is a very crucial point.

When we began our work on the nature of this antibody, and showed that it cross-reacted with other cancers, this raised several problems for us. For instance, we decided to investigate the antibody with respect to antibodies that are known serologically in human diseases, and we have found that some of these positive sera do have heterophile antibody.

Now, I'm sure this statement does not surprise many of you, because you will recall that Dr. Rapaport has indicated that in transplantation patients, there are heterophile antibodies. But we also became aware of the work of Dr. Tönder, who found that tumor tissue in 92 of 100 patients had a receptor that reacted with the Fc fragment of antibody. I want to stress that the tissue reacts with this fragment of the antibody that distinguishes globulin of man from monkey, and so forth, rather than with the conventional Fab, or antibody reactive end.

Dr. Estes, of our laboratory, has looked into that point. So far we have treated five patients' sera with pepsin to destroy the Fc fragment, and the sera still react with the BCA, the breast cancer antigen. Thus it would appear that ours is a classical antigen-antibody reaction.

The importance of that point, however, should be stressed; i.e., the classic reaction of cytotoxic antibody is against a receptoron the cell membrane, the so-called tumor associated antigen receptor, and, of course one of them gets cytolysis. Further, all of 15 tumors checked at Kansas have this receptor that reacts with the Fc fragment of antibody; hence this may be the key problem with immune surveillance and with so-called blocking factor.

In answering Dr. Cole's question, I must call your attention to a subtle point in our data. As you know, Dr. Crile has said, "You save the nodes because the memory is there," and, of course, I would remind you that 50% of these women, after they have their axillary nodes removed, have demonstrable antibody.

We've removed the cancer, and they still have some memory. Hence, we conclude the memory is central now (also from animal work in the literature).

Dr. Byrd's questions, ironically, is timely because we have studied the sera of two patients with inflammatory carcinoma of the breast. Please note, I do not want to confuse you with the table on survival, as those data were just for patients who were undergoing curative resection. One patient was sent to us with recurrent inflammatory carcinoma of the breast and had no antibody at that time. We did an adrenalectomy, and her tumor regressed, and antibody appeared. It is 18 months later and she is in complete remission, and has antibody. So there is a clinical correlation, and I would think inflammatory carcinoma of the breast may be a key type in this respect.

The histologic appearance of the tumors did not correlate in any way with the appearance of antibody, and the lymphocytes, I suspect, were trafficking in from more centrally located nodes, and/or the spleen. We are looking at that particular aspect of histology, and hope to present the data later on.

In closing, I would like to say that I do believe in preserving the beauty of our environment. I would like to say, however, that as beautiful as the female breast might be, it certainly is not very beautiful on a dead patient. And I would offer, that until we get scientific data, we should be doing some type of radical mastectomy as the lifesaving therapy of choice, rather than the emotional therapy to help the environment. Thank you very much.

Hypoglycemia and Insular Hyperplasia:

Review of 148 Cases

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ANTONIO BASOLI, M.D.

On the bases of personal experience and the series of 148 cases from an international inquiry and a review of the literature, the relation between insular hyperplasia and hypoglycemia was examined. The fundamental points in this investigation included: age, diagnostic investigations, histological findings and postoperative results. The data on the patients with insular hyperplasia indicates that 83% were of adult age. Insular hyperplasia was the only abnormal factor determined to be present. Through treatment a high percentage of cases (71%) was cured. From a practical surgical point of view, differentiation between occult insulomas and insular hyperplasia is not critical. Consequently, good results can be achieved in both diseases by practicing a progressive blind resection guided by examination of the operated specimen and by intra-operative blood sugar levels.

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HYPERINSULINISM of pancreatic origin may be caused by either a benign β cell adenoma, carcinoma, or diffuse hyperplasia of the islet cells. Of these causes, the adenoma is by far the most common.

Occasionally however, the only recognizable pathologic lesion in the pancreas is islet hyperplasia. Many cases of hypoglycemia with islet hyperplasia have been reported. Some authors hesitate to accept islet cell hyperplasia as the cause of hypoglycemia. When only diffuse hyperplasia of the islets is found they feel that the hypoglycemia is caused by a missed insuloma. In the child, however, the existence of islet hyperplasia and its capacity to determine hypoglycemia is generally accepted.[42] Cases have been reported in which pancreatic hypoglycemia exists with insular hyperplasia in the absence of insulomas and other hypoglycemia-inducing diseases.[29] Many authors have reported relief of hypoglycemia after pancreatic resections without finding a beta islet-cell tumor.[36,44,49,63]

Our experience in management of hyperinsulinism of pancreatic origin consists of 11 adenomas, one carcinoma and five insular hyperplasias. The observation of these cases of hyperplasia induced us to investigate this still much discussed topic. We reviewed the literature and carried out an international inquiry (Table 1). An analysis of these cases and of our own experience is reported in this paper.

Material

On the basis of our research we observed that of a total of 1137 cases of organic hypoglycemia, 1067 (93.8%) were caused by insulomas and 70 (6.2%) by insular hyperplasia. In seven cases (0.6%) there was a combination of the two diseases.

Of the 149 authors who communicated their experience on hypoglycemia of pancreatic origin, 30 (20%) report cases of insular hyperplasia. Yet seven (4%) of these have doubts on the connection between hypoglycemia and insular hyperplasia in their patients.

Of 148 cases of insular hyperplasia documented from a histological and clinical point of view, 122 had undergone surgical intervention with immediate and long term relief of hypoglycemia.

In the series collected from 140 cases documented, there were 78 (56%) females and 62 (44%) males: only 16 were children, while all the others were adults with an age ranging from 19 to 65 years.

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TABLE 1. *Insular Hyperplasias: Case Material*

Series	No. of Cases	Authors (cases)
Gathered by Internat. Inquiry	65	Biancalana 1, Blomquist 1, Bloodworth 1, Carrington 1, Creutzfeldt 1, De Cesare 1, De Peyster 5, Fonkalsrud 1, Fraser 1, Fuchsig 2, Goffrini 3, Hess 1, Huguet 1, Juvara 7, Leger 15, Mandache 1, McGarity 1, McGovern 1, Passaro 1, Pellegrini 1, Poli 1, Porter 6, Ritchie 1, Saegesser 1, Sato 2, Shamiyeh 1, Singleton 1, Solcia 1, White 3, Zenker 1
Gathered from Review of the Literature	78	Auguston 1,[1] Barbarino 1,[2] Becker 6,[3–4] Bell 1,[5] Bernhard 3,[6] Boone 1,[7] Broc 6,[9] Callaway 1,[10] Conn 1,[11] David 1,[12] Deucher 2,[14] Deuil 1,[15] Edwards 1,[16] Fish 1,[17] Geraud 1,[19] Gilchrist 1,[29] Graham 1,[21] Greenle 1,[22] Grotzinger 2,[23] Haworth 8,[25] Hellstrom 1,[26] Hill 1,[27] Holman 1,[28] Kalbfleisch 1,[30] Kjaergaard 2,[32] Koutras 4,[33] Leriche 1,[37] Linder 1,[38] McCaughan 4,[39–40] Magner 1,[43] Martin 1,[46] Maxeiner 1,[47] Mengoli 1,[43] Milone 1,[49] Mosenthal 1,[50] Orr 1,[52] Pfeiffer 1,[53] Phillips 1,[54] Richardson 1,[55] Sawyer 1,[57] Sendrail 2,[59] Simon 1,[60] Sloper 2,[61] Spencer 1.[62] Walters 1,[64] Whipple 3[65]
Personal Cases	5	
Total	148	

Our patients had an average age of 35 years. Four were females and one was a male.

The symptomatology of our cases with insular hyperplasia was practically the same as that presented by patients with insulomas. The only conclusion we can draw from our experience is that, in comparison to insulomas, patients with hyperplasia presented hypoglycemia crises at less frequent intervals. However, cardiovascular and gastrointestinal symptoms were more often noted (Table 2). Neurological symptoms were frequent and often resulted in diagnostic errors, with admittance of patients to mental hospitals. Gastrointestinal symptoms, consisted mainly in hunger while the cardiovascular symptoms consisted mainly of sinus tachycardia.

On the average, there elapsed four-and-a-half years from the onset of symptoms to the diagnosis of hypoglycemia. Epilepsy was diagnosed three times and numerous E.E.G.'s were carried out with negative results.

The same investigations were useful in evaluating patients with hyperplasia and in those with insulomas. In particular, the prolonged fasting test (five out of five) and the tolbutamide test (three out of four) had a high degree of diagnostic accuracy. Blood insulin levels, measured by radioimmunological assay, were very high in the three cases tested. The clinical symptoms and the biochemical data of our patients do not differ greatly from those communicated to us by the authors. Twenty-one reported that in their opinion, clinical findings and laboratory data showed no differences between their cases of insulomas and those of hyperplasia.

The surgical treatment of our patients is summarized in Table 3. The preoperative diagnosis in our patients has always been that of hypoglycemia from insuloma and the finding of insular hyperplasia was unexpected.

The type of intervention, the death rate, and longterm results which were obtained from the different authors, are summarized in Table 4. The types of operation most used were corpocaudal pancreatectomy (63.8%) and subtotal pancreatectomy (24.3%). Twice, following a subtotal resection, a total resection was carried out with recovery in one case and the persistence of hypoglycemia in the other. The follow up period was of six months to five years except in five cases. Pancreatic biopsy led to the diagnosis of insular hyperplasia in four cases. One of these cases had insular carcinoma associated with hyperplasia.

In four cases, insular hyperplasia was diagnosed at post-mortem examination.

Case Report

L.G., a 32-year-old woman had experienced increasingly frequent episodes of weakness, memory loss, mental confusion and coma over a 5-year period.

Her symptoms were most prominent when fasting and after physical effort. The first physician she consulted diagnosed epilepsy. She was admitted to the 2nd Surgical Clinic of the University of Rome in September 1969. There were no significant physical findings, except tachycardia during hypoglycemic attacks. An oral glucose tolerance test, tolbutamide test, prolonged fasting

TABLE 2. *Insular Hyperplasias: Symptoms and Diagnosis (personal cases)*

Case	Age	Sex	Principal Symptoms	Previous Diagnosis	Previous Admissions	Blood Sugar	IRI	Fasting	Tolbutamide
1	50	M	5 years neuropsychic cardiovascular	epilepsy	2	0.30		+	
2	39	F	11 years neuropsychic	epilepsy	4	0.40		+	+
3	36	F	7 months neuropsychic gastrointest.			0.45	69	+	±
4	32	F	4 years neuropsychic cardiovascular	epilepsy	3	0.25	91	+	+
5	20	F	4 years neuropsychic cardiovascular gastrointest.		1	0.40	72	+	+

TABLE 3. *Insular Hyperplasias: Interventions and Results (personal cases)*

Case	Type of Intervention	Mortality	Postoperative Glycemia 1st	3rd	6th	Long-Term Results
1	blind distal resection		1.80	1.20	1	cure at 1 year, paradiabetic
2	blind distal resection		2	1.50	1	cure at 1 year
3	blind distal resection		0.80	0.80	0.60	hypoglycemia
	subtotal pancreatectomy		2	0.95	1.10	cure at 6 months, paradiabetic
4	blind distal resection		1.60	1.30	0.90	cure at 1 1/2 years
5	blind distal resection		1.95	1.20	0.95	cure at 9 months

test and glucagon test were diagnostic of functioning beta cell tumor of the pancreas.

The fasting serum insulin level was elevated at $91\mu U/ml$. On November 22, 1969 she underwent exploratory laparotomy. The pancreas and sites of aberrant pancreatic tissue were carefully examined and no tumor could be found. Therefore, a blind distal resection was performed. Histological examination of resected specimen showed insular hyperplasia (Figs. 1 and 2). Her blood sugar rose to 160 mg/100 on the first postoperative day and gradually returned to normal by the 6th day. She was discharged on the 18th postoperative day. She has had no recurrence of hypoglycemia and has done well over a three-year period of followup.

Discussion

The diagnostic and therapeutic problems of insular hyperplasia are not very different from those of occult insulomas. From a clinical and biochemical point of view it is not possible to differentiate the two diseases. The only possible way might be selective arteriography which, in spite of the high percentage of success (66% in our inquiry), may not always demonstrate a tumor of small dimension and of sparse vascularity.

As for surgical treatment, at present a progressive resection of the pancreas guided by the blood sugar levels and by histological examination of the removed specimen is advised by some authors in the management of occult insulomas[13,24,31,41] rather than blind distal resection.

This procedure can also be successfully applied in cases of insular hyperplasia. Exploration of the pancreas and common sites of aberrant pancreatic tissue should be carried out as there exists, though rarely, the possibility of a hyperplasia-insuloma association.

Therefore, from a practical point of view, in the absence of a tumor a blind resection should be carried out, this will have a beneficial effect in both diseases.

From the analysis of our patients and of the series gathered, the relationship between hypoglycemia and insular hyperplasia appears well demonstrated.

There were five points noted in the majority of the collected cases: 1) adult age; 2) absence of other diseases producing hypoglycemia; 3) positive diagnostic tests for organic hypoglycemia; 4) histological findings of insular hyperplasia; and 5) recovery after operative resection of the pancreas.

Regarding the first point, only 16 cases (13%) concerned children. Four of these were communicated to us by Porter who, on the bases of his cases, doubts any connection between hyperplasia and hypoglycemia. The average age of the subjects taken into consideration was 39 years and 6 months; this was only slightly lower than our patients with insulomas (45 years and six months).

The possibility that other pancreatic and extrapancreatic diseases may cause hypoglycemia is generally accepted.

Chronic pancreatitis complicated by the presence of hypoglycemia, is reported in the literature.[18,34,36,56] However, these reports lack histological confirmation. Moreover it cannot be excluded that some of these cases should be interpreted as examples of functional hyperinsulinism. In chronic pancreatitis hypoglycemia has been attibuted to an obstruction of the excretory ducts with a consequent hypertension effect.[45] The observations of recovery with simple sphincterotomy,[34] external biliary drainage,[44] or with simple cholecystectomy[58] cast

TABLE 4. *Insular Hyperplasias: Interventions and Results (115 completely documented cases)*

	No. of Cases	%	Mortality No. of Cases	%	Long-Term Results* Poor No. of Cases	%	Fair No. of Cases	%	Good No. of Cases	%
Caudal Pancreatectomy	5	4.4							4	80
Corpocaudal Pancreatectomy	76	66	2	2.7	9	11.8	9	11.8	53	69.8
Subtotal Pancreatectomy	29	25.2	1	3.4	4	13.7	1	3.4	22	75.7
Laparotomy	5	4.4	1	20	4	80				

* In 5 cases long-term results were not specified.

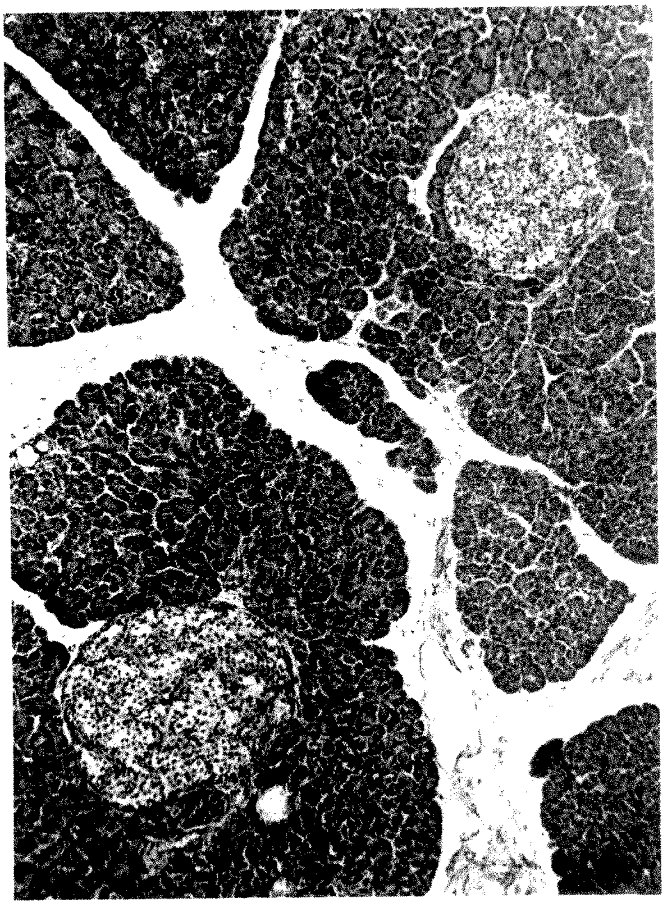
doubts on organic hypoglycemia as the cause of hypoglycemia in these patients.

Extrapancreatic tumors, such as mesenchymal tumors, hepatomas, pseudomyxomas, epithelial tumors and those of the adrenal cortex, are important and convincing causes of hypoglycemia.

In these cases the differential diagnosis can often be made by routine x-ray investigations. Also the plasma insulin levels are normal during fasting and during an oral glucose tolerance test. In 84 mesenchymal tumors, 40 hepatomas, 19 adrenal cortex tumors, and 13 epithelial tumors, the only exception was a patient reported by Oleesky in 1962.[51] The patient was a male of 62 years with pelvic spindle cell fibrosarcoma. The insulin level was 860/ml and blood sugar 23 mg%. This hypoglycemia disappeared after radiotherapy.

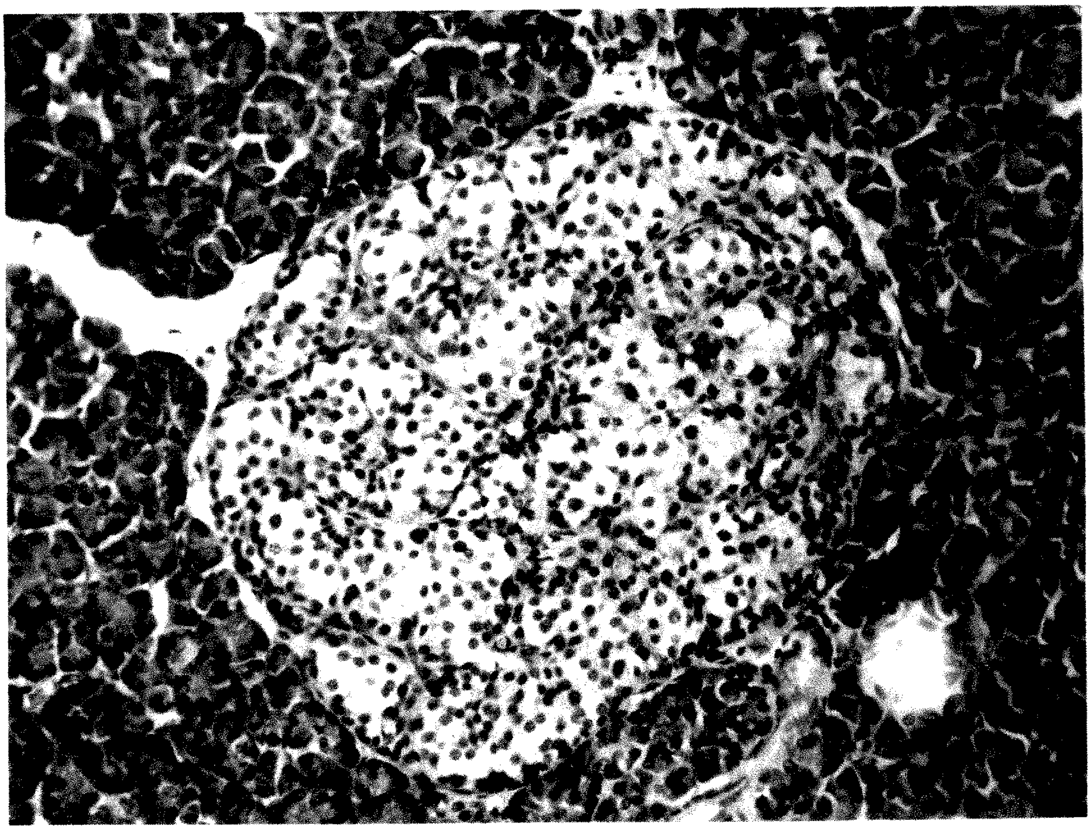
Functional hypoglycemias from other diseases of the digestive system are easily distinguishable from organic pancreatic ones. In fact, provocative tests are sufficient to exclude this possibility.

The histological examination carried out on 144 operated and four autopsy specimens, allows the demonstration of hyperplasia, occult insulomas, or chronic pancreatitis. The pathological findings also demonstrate that in six cases an adenoma was associated with insular hyperplasia. In one case, hyperplasia co-existed with an inoperable carcinoma. In two cases, hyperplasia and insuloma were treated at the same time and in two cases a blind distal resection was followed by enucleation of the adenoma. In one case, operation for the adenoma



1a.

FIGS. 1a. and 1b. Case 4. Histological examination of resected specimen. Fig. 1a shows an increase in number of islet of Langerhans (×60). Fig. 1b shows an increase in size (×250).



1b.

was carried out and subsequently reoperation with the diagnosis of hyperplasia. The long term results in this group of patients, records two failures; one of which related to exploratory laparotomy for insular carcinoma, and five recoveries.

Considering the results of surgical treatment the percentage of recoveries were 71%. Mortality of operation was 4.5%. In many cases, surgical failure, after corpocaudal resection can be attributed to an inadequate resection of the pancreas. Yet one cannot deny that occult insulomas could have been present in the 24.5% of the cases where hypoglycemia persisted.

Acknowledgments

We are greatly indebted to all those authors who sent us their personal communications and to all those who collaborated with their valid information.

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Atypical Fibromuscular Hyperplasia Involving the Carotid Artery

WILLIAM GEE, M.D., ROBERT BURTON, M.D., RONALD J. STONEY, M.D.

A case of atypical fibromuscular hyperplasia involving the carotid artery in a 38-year-old male is described. The lesion, with associated intimal disruption and subintimal hematoma, caused cerebral embolus and transient neurologic dysfunction. Segmental resection and autogenous graft reconstruction of the carotid artery were successful in removing the lesion and preventing subsequent symptoms.

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FIBROMUSCULAR HYPERPLASIA involving the cervical internal carotid artery has been recognized as a cause of cerebrovascular insufficiency since 1965.[1,2,4] The initial treatment consisted of resection of localized zones of typical diaphragmatic stenoses and reconstruction of the carotid artery with autogenous techniques. In 1968 Morris *et al.*,[3] advocated graduated intraluminal dilatation for more diffuse involvement in which multiple stenoses occurred in the extracranial portion of the internal carotid artery. Cerebrovascular insufficiency was manifested by transient neurologic disturbances assumed to be due to impaired perfusion through critical arterial stenoses. In some patients a frank stroke occurred following thrombosis of the involved internal carotid artery. Intimal disruption with subintimal dissecting hematoma caused arterial occlusion in these patients.

In the present report, atypical localized fibromuscular hyperplasia with subintimal hematoma of the carotid artery appeared to be the source of a cerebral embolus, resulting in a transient neurologic disturbance.

Case Report

A 38-year-old normotensive male had a single 12-hour episode of right hemiparesis with complete resolution. There were no ocular manifestations. Three weeks later, the results of a complete neurologic and vascular examination were normal. The carotid arteriogram showed a cleftlike defect in the wall of the left internal carotid artery (Fig. 1a). At operation a bluish papule 3 mm in diameter was found at the corresponding site on the wall of the internal carotid artery. No atheromata were noted. The proximal 2 cm of the internal carotid artery containing the lesion were resected and arterial continuity was restored by interposing an autogenous saphenous vein graft. Postoperative recovery was uneventful, and the patient has been free of symptoms for the past year. An arteriogram taken six months after operation showed a patent reconstruction (Fig. 1b). Renal arteriograms disclosed no evidence of fibromuscular hyperplasia in these vessels.

Pathologic examination of the resected specimen showed a transverse intimal laceration with subintimal hematoma and thrombosis (Fig. 2). Microscopic sections showed hypertrophy of the intima with disruption. A subjacent organizing hematoma and medial hyperplasia were noted, which are characteristic of focal fibromuscular hyperplasia, (Figs. 3, 4).

Discussion

This case is atypical of carotid fibromuscular hyperplasia for several reasons. First, the patient was male, and this type of arterial dysplasia has an unusual sex distribution in which women outnumber men (five to one) in all arterial sites thus far reported. Second, cerebral ischemia was caused by an embolus rather than by impaired perfusion resulting from arterial stenosis. This case is apparently the first to be reported in which this form of organ ischemia has been described in this arterial dysplasia. Third, the arteriographic manifestations were occult, suggesting that we should re-examine our usual arteriographic criteria for fibromuscular hyperplasia. Fourth, the arterial involvement was localized and accessible, permitting resection and graft replacement.

The features emphasized in this case should alert us to carefully scrutinize patients with cerebral ischemic syndromes for atypical, but correctable, extracranial arterial pathology.

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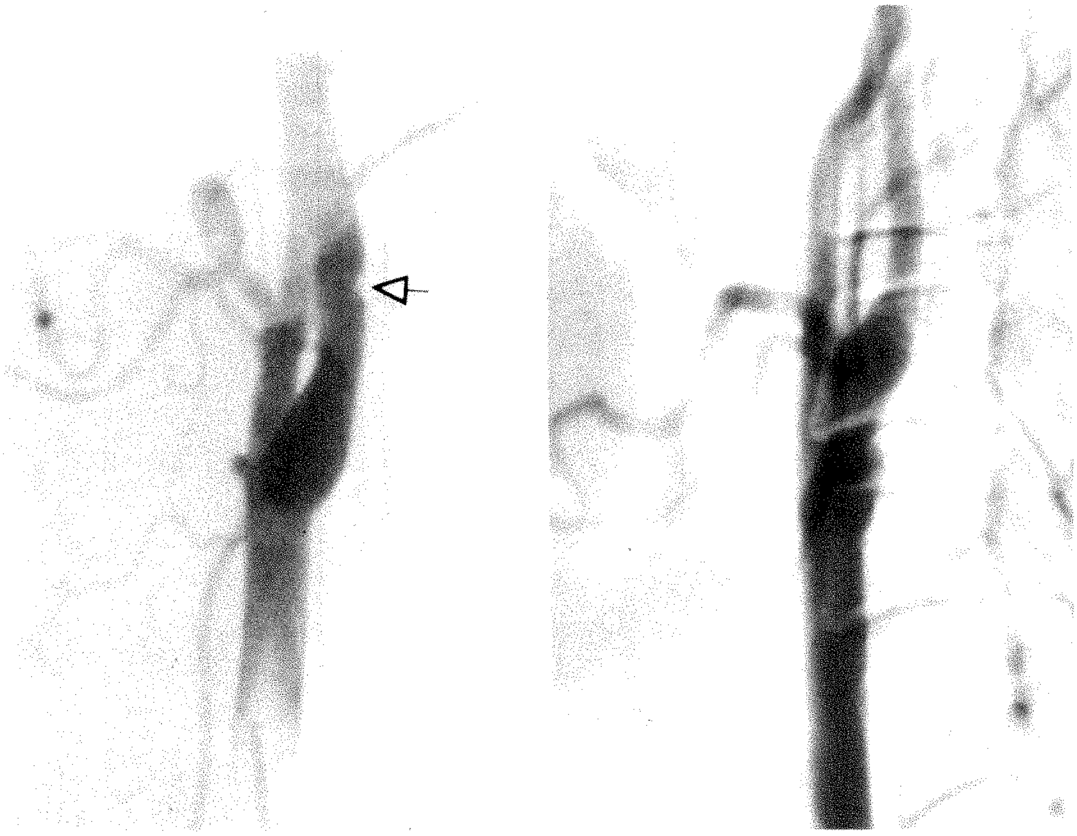

FIG. 1a, b. Selective left carotid arteriograms. Fig. 1a. (Left) Preoperative arteriogram. Arrow indicates defect. Fig. 1b. (Right) Postoperative arteriogram shows patent reconstruction.

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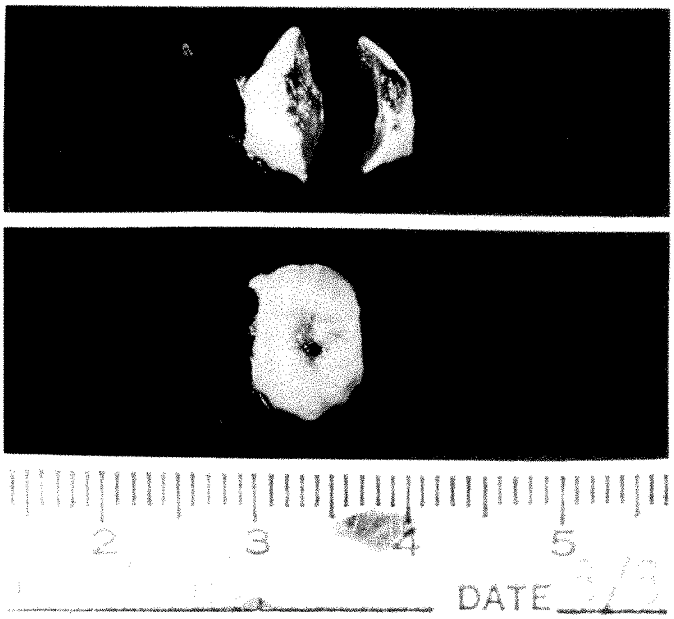

FIG. 2. Resected specimen of left carotid artery. (Top) Longitudinal section through artery wall showing subintimal hematoma. (Bottom) View of intimal surface showing intimal defect (center) with hematoma beneath.

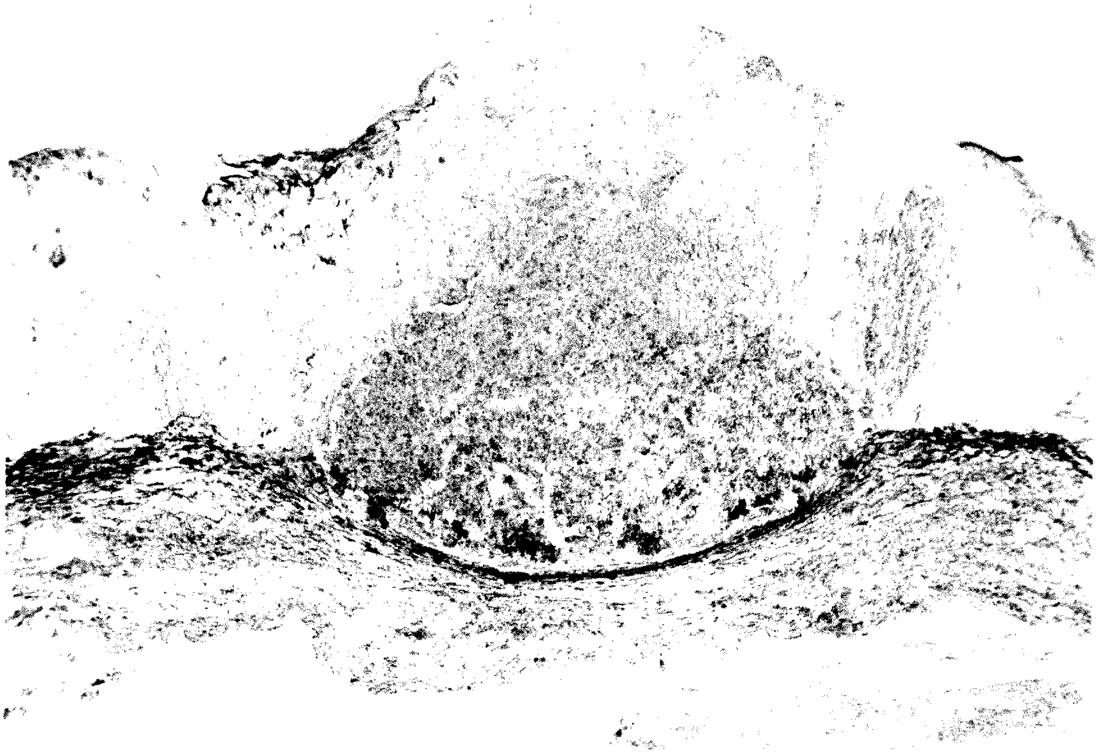

FIG. 3. Photomicrograph of artery wall. Note intimal hypertrophy and organizing hematoma.

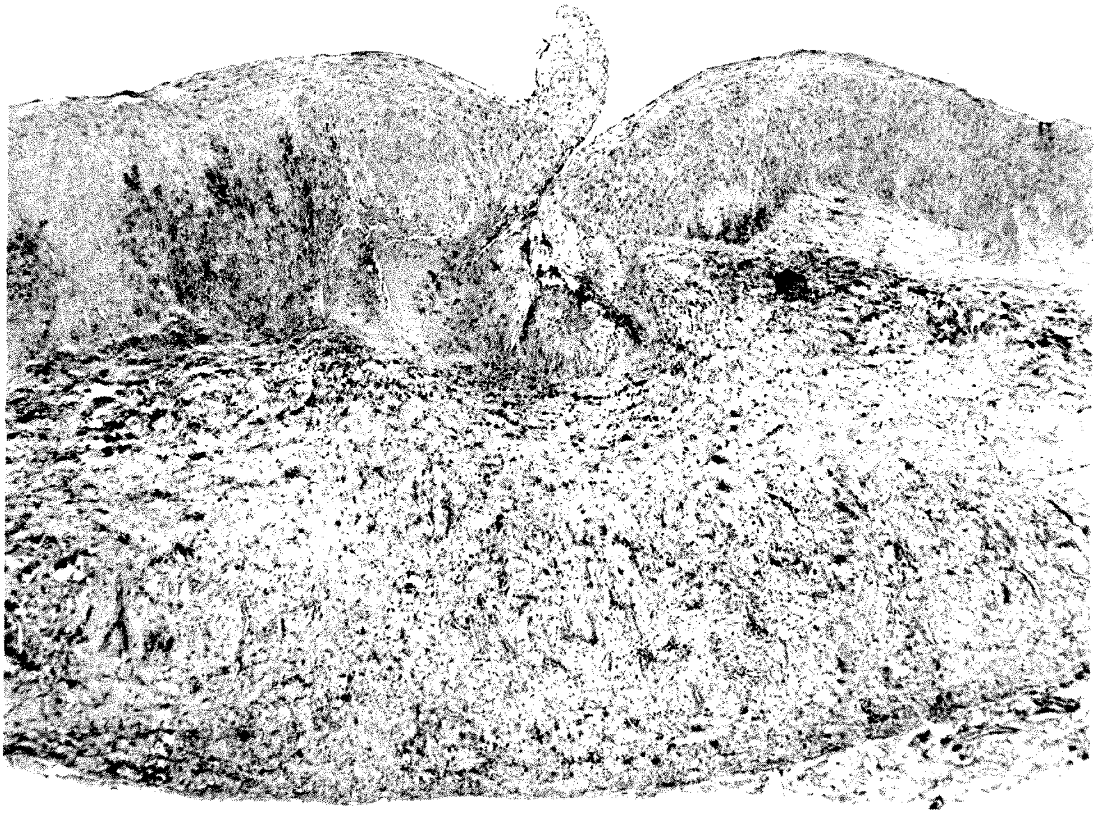

FIG. 4. Photomicrograph showing internal cleft and medial hyperplasia.

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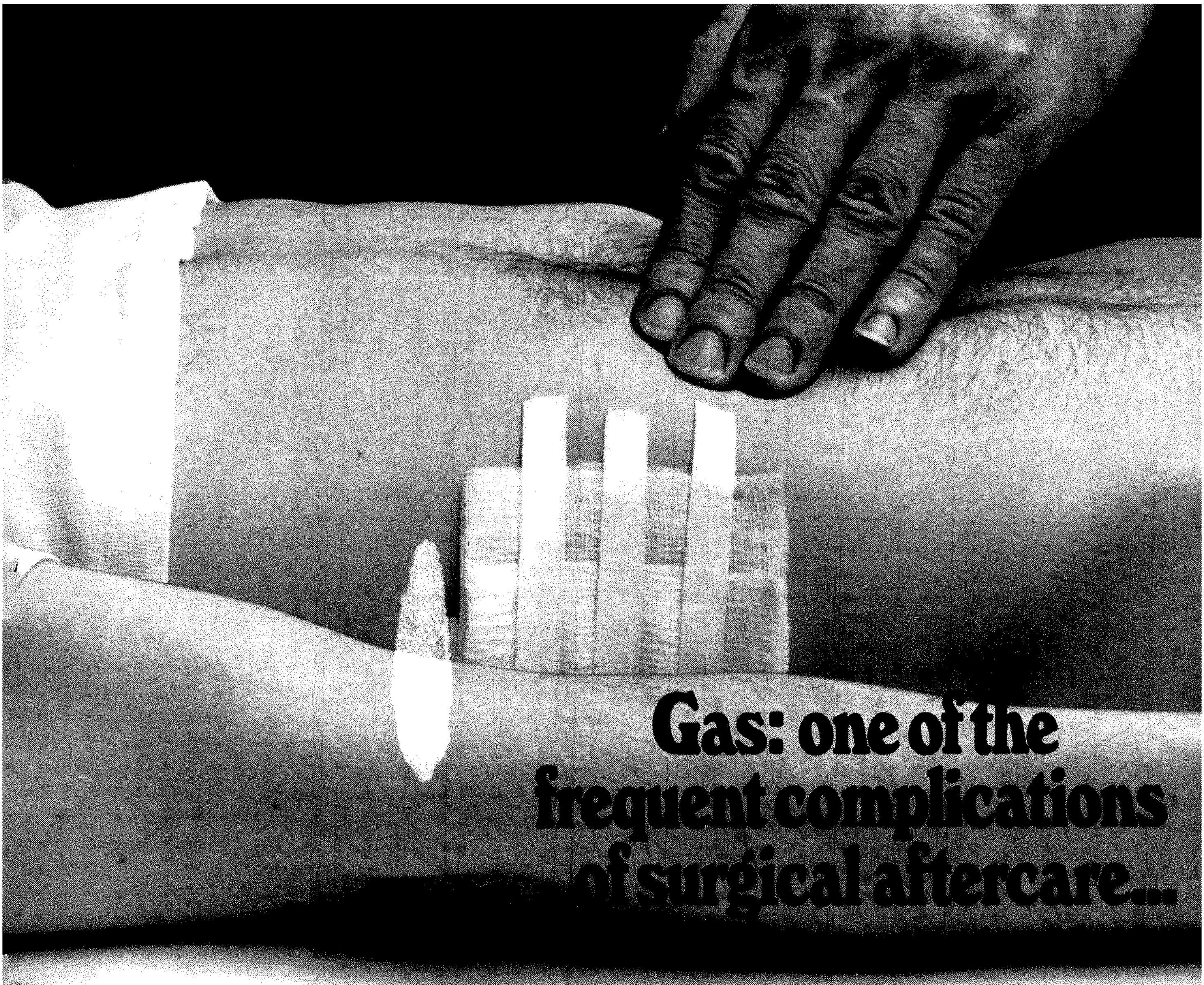
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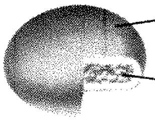

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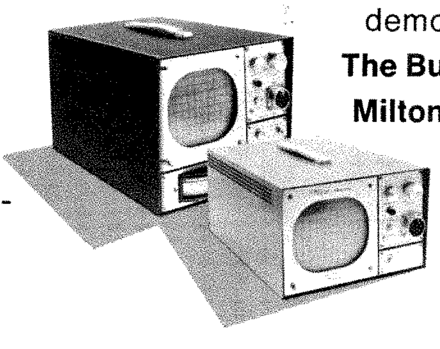

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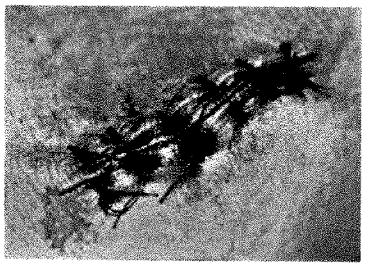

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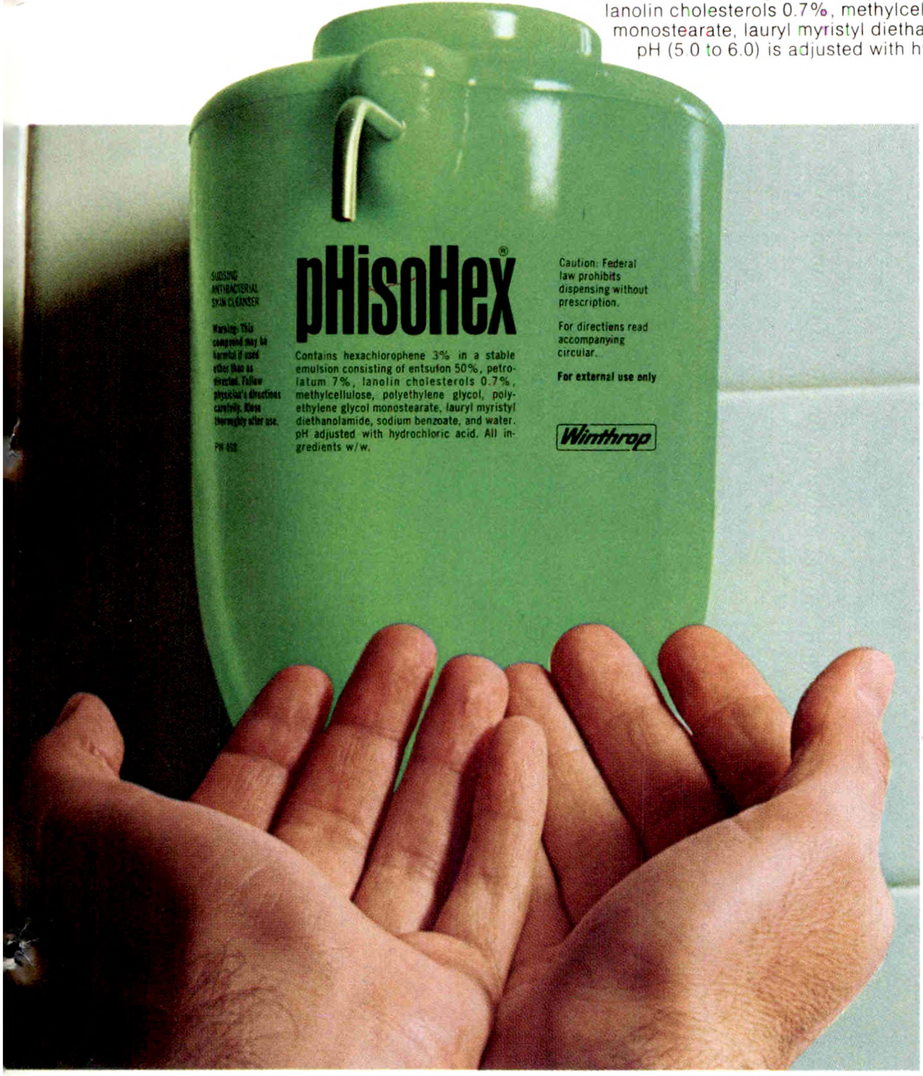
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pHisoHex contains 3% hexachlorophene with cumulative antibacterial action on the hands, unique among antibacterial agents.

Why is this important?

pHisoHex continues to protect during the interim between scrubs if used regularly as directed.

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While more frequent washing with other agents is an alternative, it is not a practical one for prolonged surgery.

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Nonalkaline, hypoallergenic pHisoHex is clearly indicated for staphylococci and other gram-positive bacteria as a bacteriostatic hand cleanser and surgical scrub. ***Rinse thoroughly after use.***

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Actions: pHisoHex has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control. (See Warnings.)

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions. Vacuolization has been reported, with a symmetrical, rostrocaudal distribution in the brainstem reticular formation of premature infants of low birth weight, especially those with skin rashes and wounds, who were washed with 3% hexachlorophene. However, the clinical correlates of such vacuolization have not been established since these infants also had critical clinical conditions or pathologic findings of independent etiology. Some recent opinions express particular concern with respect to the use of pHisoHex on premature infants. Although the scientific picture is still incomplete, pHisoHex should not be used on premature infants unless, in the judgment of the prescribing physician, its use is required by the unique circumstances of an individual case.

When preparations containing hexachlorophene are left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms.

PHISOHEX SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin, or exposure to a powder accidentally containing approximately 6.5% hexachlorophene.

Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only*. If swallowed, pHisoHex is harmful, especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precaution: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, plastic bottles of 1 gallon, and ¼ oz. (8 ml.) unit packets, boxes of 50. pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts.

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Winthrop Laboratories
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(1626A)

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125 mg. and 250 mg.**
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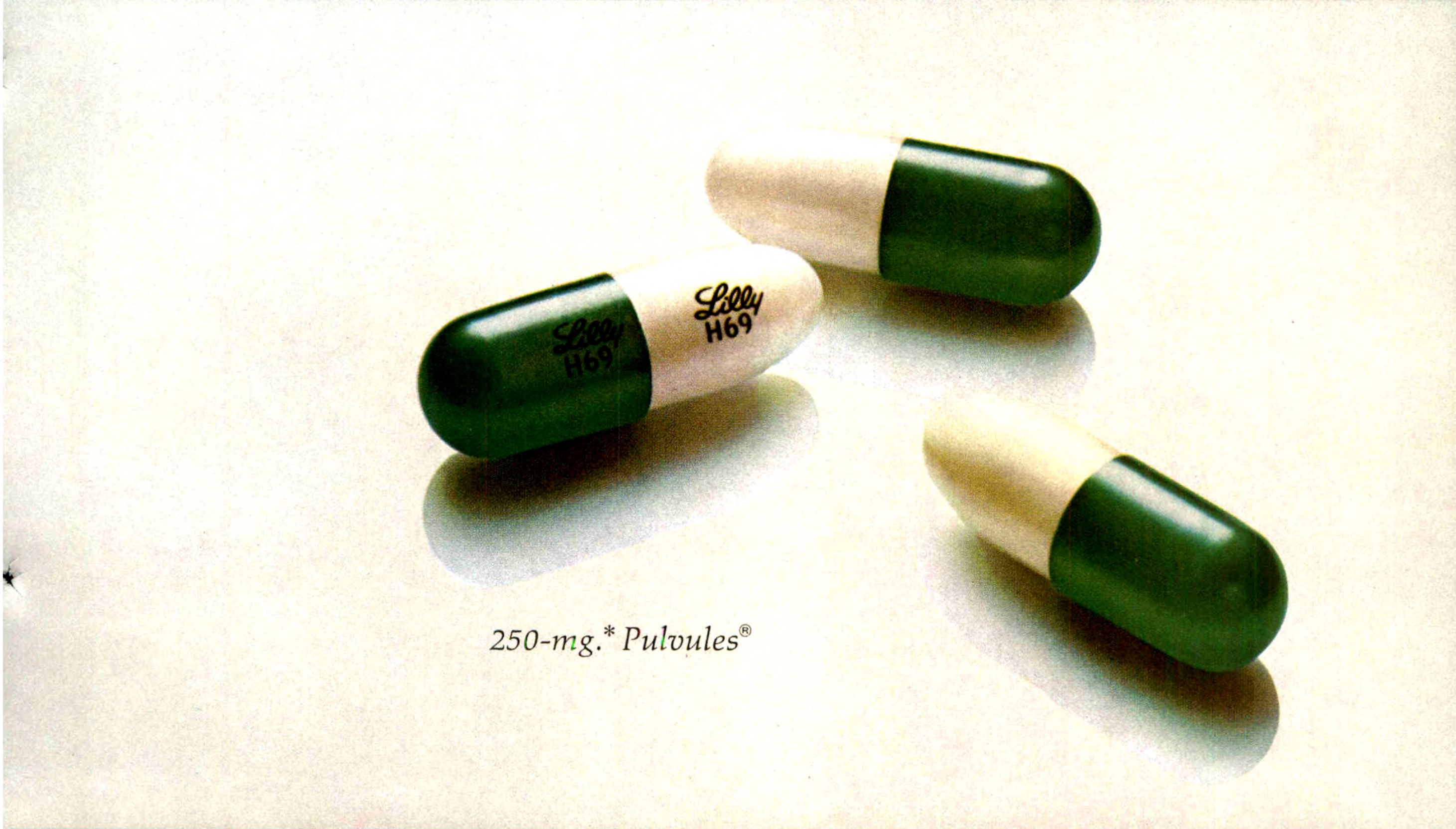

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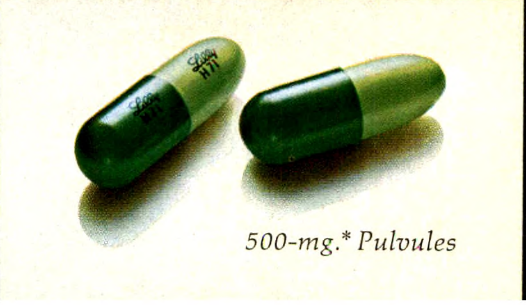

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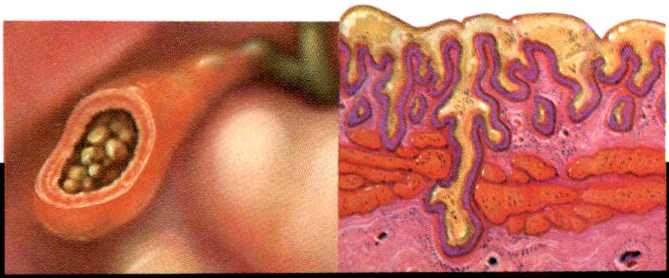
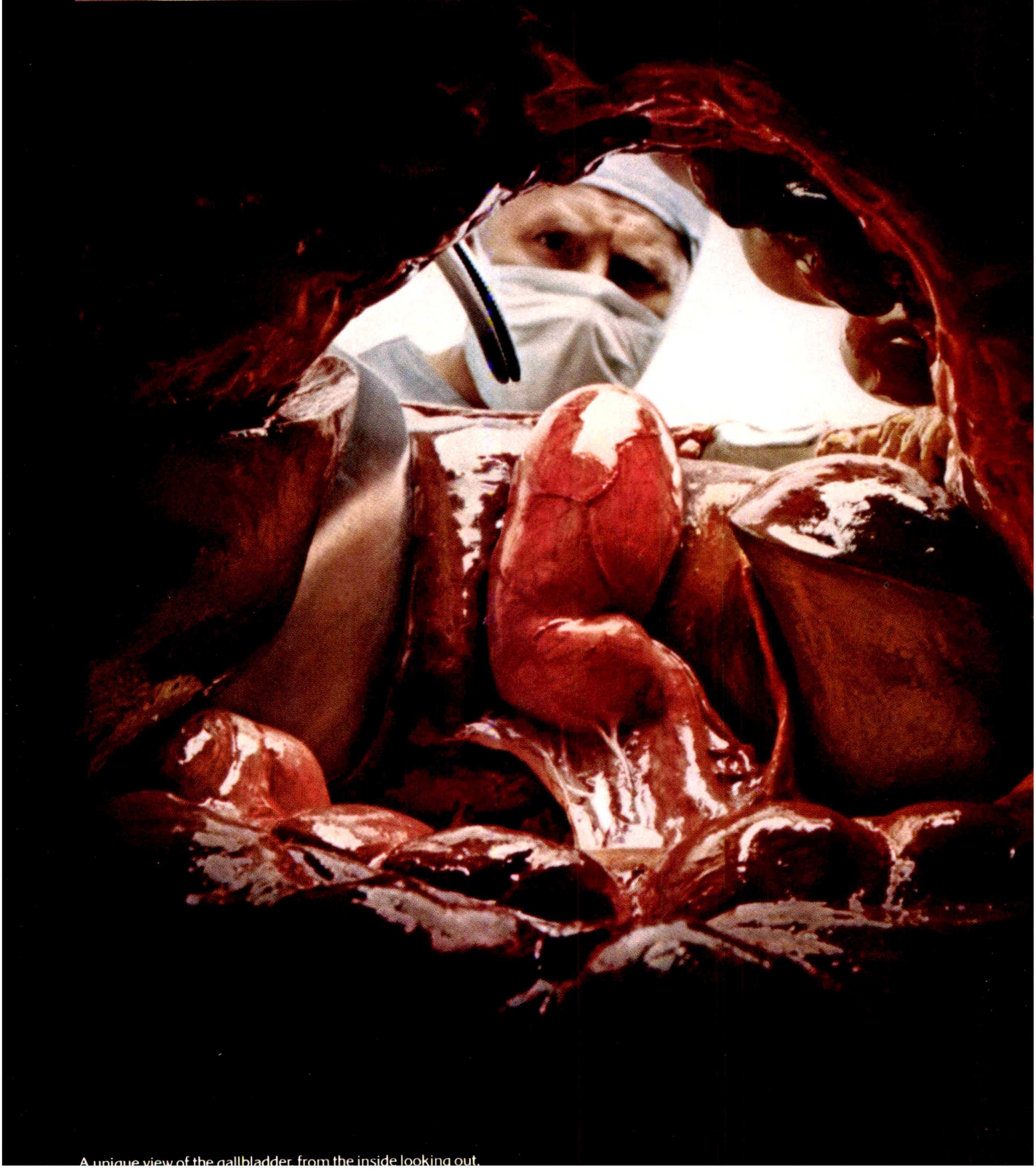
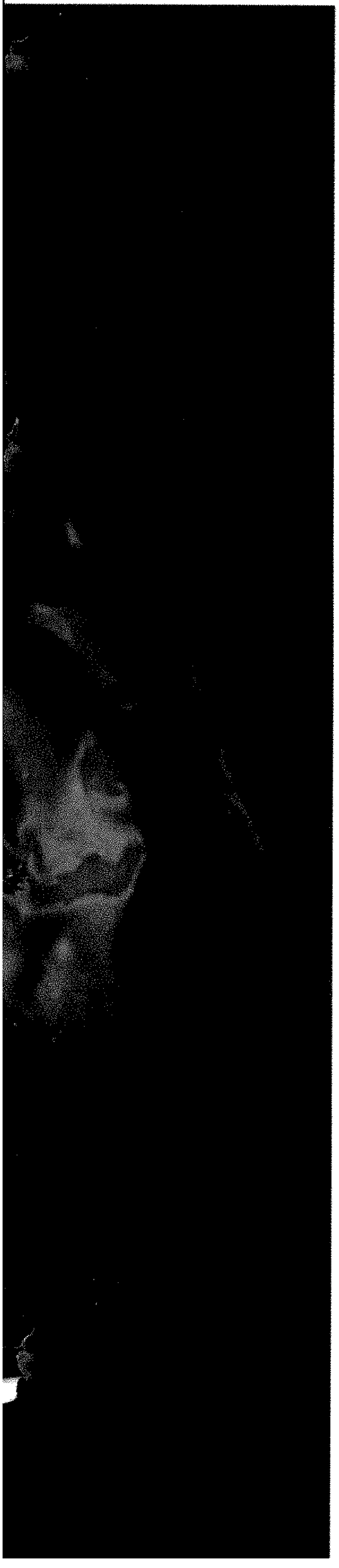


1. Artist's conception of cutaway view of gallbladder containing stones which, by causing irritation of the organ's interior wall and restricting biliary flow, may play a role in the repeated episodes of inflammation and infection associated with chronic cholecystitis.
2. Artist's conception of microscopic section of gallbladder wall showing chronic state with superimposition of inflammation, edema and necrosis due to an acute episode.



A unique view of the gallbladder, from the inside looking out.



Cholecystitis from the pathogen's point of view

Vibramycin (doxycycline) penetrates gallbladder tissue to reach susceptible[1] pathogens

Vibramycin can be useful in cholecystitis because it provides a wide antibacterial spectrum and therapeutic tissue concentrations.[2] Vibramycin is active against susceptible[1] strains of bacteria including Escherichia coli and Enterobacter aerogenes (formerly Aerobacter aerogenes).

Concentrations of oral Vibramycin in gallbladder tissue removed from four surgical patients on a dosage of 200 mg. P.O. stat and 100 mg. P.O. once daily until surgery.[2]

Patient No.	Concentration in Tissue (mcg./Gm.)
1	5.80[3]
2	1.58
3	8.68
4	7.73

---

[1] Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

[2] Fabre, J. et al.: Schweiz. Med. Wochenschr. 97:915, May 17, 1967.

[3] Concentration in the bile taken simultaneously: 24.2 mcg./ml.

Vibramycin® I.V.

(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.
200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid.

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PFIZER INC

Penetrates tissue to reach susceptible* pathogens...

Vibramycin® I.V.

(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.
200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid.

Important facts about Vibramycin (doxycycline)

- can maintain therapeutic blood levels with a single daily infusion
- can be used without complexities of dosage alteration in patients with impaired renal function
- does not significantly elevate BUN in patients with renal insufficiency
- virtually the same broad range of indications when switching from I.V. to oral form

*Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

Vibramycin® Hyclate (doxycycline hyclate) and
Vibramycin® I.V. (doxycycline hyclate for injection)
BRIEF SUMMARY

Contraindicated: In persons hypersensitive to any of the tetracyclines.

Warnings: Use of tetracyclines during the last half of pregnancy, infancy and childhood to the age of 8 years may cause permanent discoloration of developing teeth. This is more common during long-term use of the tetracyclines but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Thus, tetracyclines should not be used in this age group unless other drugs are not likely to be effective or are contraindicated. Individuals receiving tetracycline antibiotics should be advised that direct sunlight or ultraviolet light can cause photosensitivity reactions. If these reactions (exaggerated sunburn) occur, discontinue therapy. Doxycycline forms a stable calcium complex in any bone-forming tissue. Fibula growth has been decreased in prematures given oral tetracyclines 25 mg./kg. q. 6 h., but this reaction was reversible when the drug was discontinued.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur to a significant degree with the use of Vibramycin in patients with impaired renal function.

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus. Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of Vibramycin Intravenous in children under 8 years is not recommended because

Precautions: Overgrowth of nonsusceptible organisms may occur, including fungi. If such superinfections are encountered, discontinue Vibramycin and institute appropriate therapy.

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before initiating therapy. Conduct monthly serological tests for at least 4 months.

Because tetracyclines depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, conduct periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic.

Treat all Group A beta-hemolytic streptococcal infections for at least 10 days.

Avoid giving doxycycline with penicillin because of possible interference with penicillin activity.

Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given concomitantly to patients taking oral Vibramycin.

Adverse Reactions: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, maculopapular and erythematous rashes, exfoliative dermatitis, photosensitivity, urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. Prolonged administration of tetracyclines may produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Bulging fontanels have been reported in young infants on therapeutic dosage but disappeared when the drug was discontinued. A dose-related rise in BUN has been reported.

Oral Adult and Children's Dosages: See the Vibramycin Oral package insert for recommended dosage schedules for adults and children.

Intravenous Dosage and Administration: Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg./day) differs from that of the other tetracyclines (1-2 Gm./day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that Vibramycin, at the usual recommended doses, does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Intravenous Adult Dosage: The usual dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending on the severity of infection, with 200 mg. administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg. daily for at least 10 days.

Intravenous Children's Dosage: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg./lb. of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See "Warning" Section for Usage in Children.)

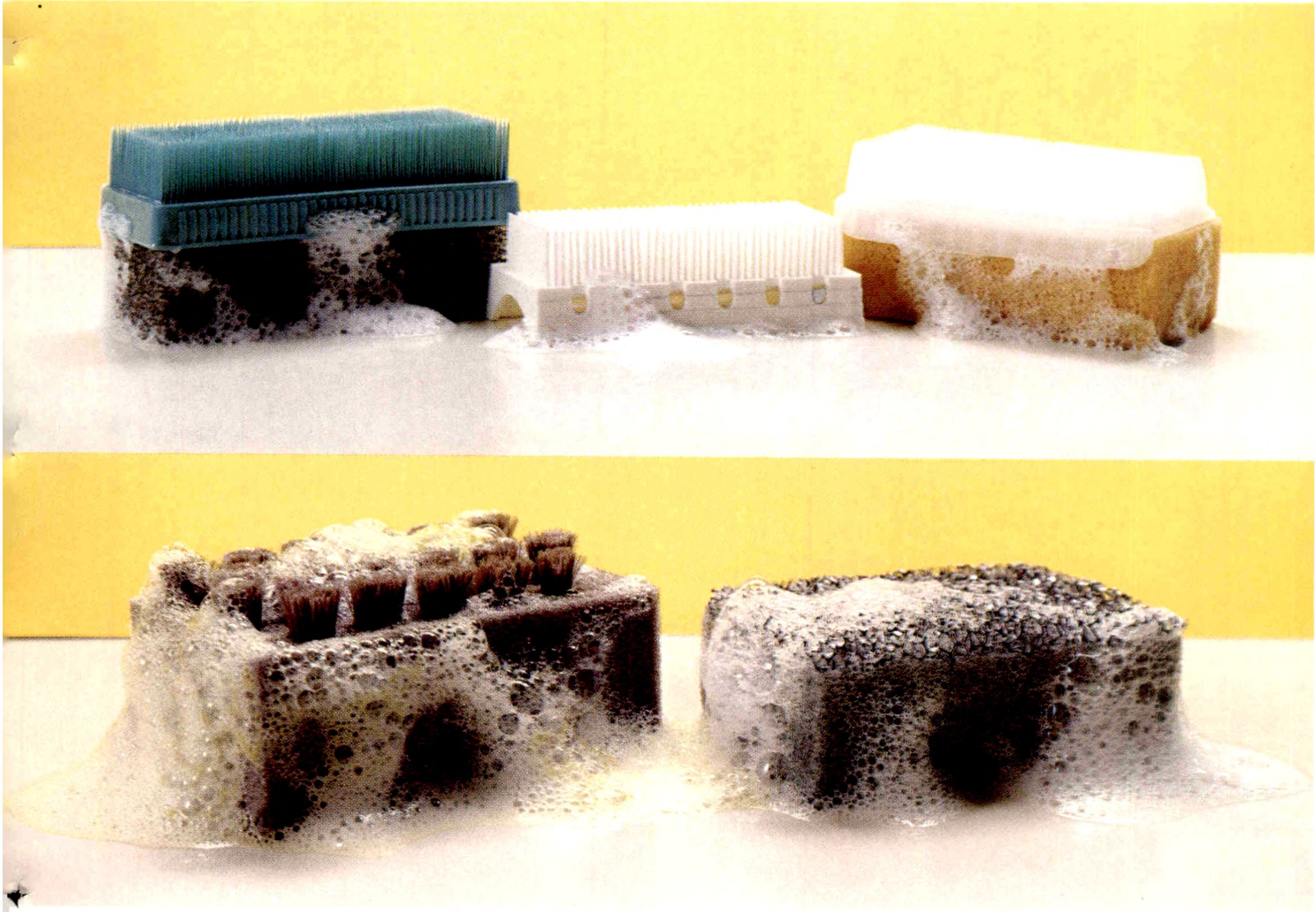
General: The duration of infusion may vary with the dose (100 to 200 mg. per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg. of a 0.5 mg./ml. solution is one hour. Desired concentrations of the final solution should be 0.2 mg./ml. to 0.5 mg./ml. Concentrations below 0.1 mg./ml. or above 1.0 mg./ml. are not recommended. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly nor subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

More detailed professional information available on request.

Pfizer LABORATORIES DIVISION

Other scrub products can't promise you everything.



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Sure, some of the other scrub products give you some of these benefits. But only PRE·OP products give you all of them. Choose either PRE·OP® Surgical Scrub Sponges or PRE·OP *plus*—the versatile sponge-brush combination that can be as firm or as soft as you wish. They're single-use products, so there's no cross-contamination. And they're economical, too. Available with either iodophor or hexachlorophene.

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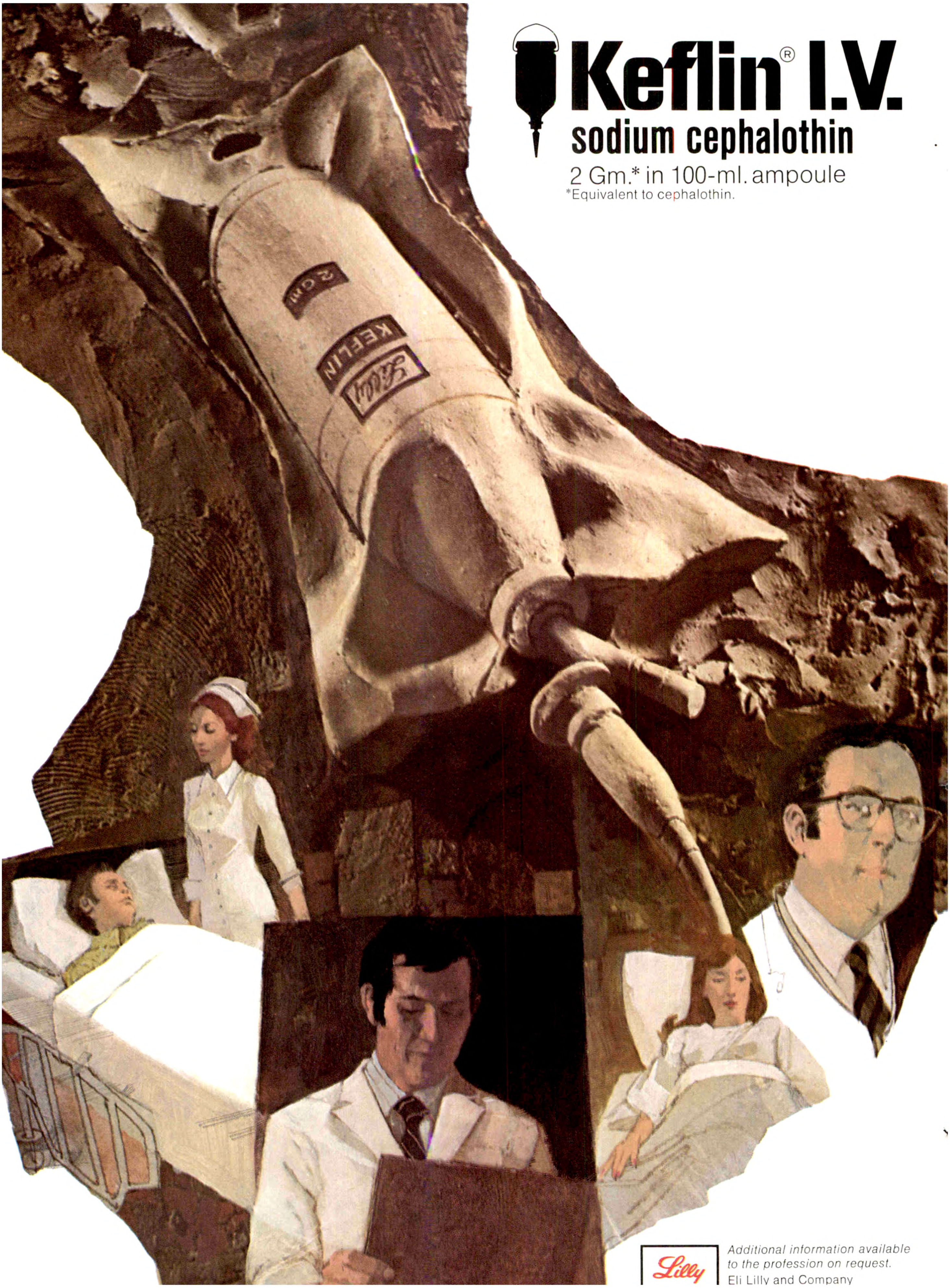

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Surgical Management of Corrosive Gastric Injuries

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Four cases of extensive corrosive gastric injury requiring surgical treatment are presented. Appropriate management of this life-threatening entity requires an awareness of its subtle presentation plus a well planned surgical approach.

MOST INGESTED CORROSIVE SUBSTANCES contain alkalis which frequently cause esophageal burns and strictures, and only occasionally produce gastric injury. In contrast, acid ingestions usually spare the esophagus but often burn the stomach.

The following reports represent our personal experience with four cases of extensive gastric burns resulting from the ingestion of corrosive materials and requiring acute and long term surgical management.

Case Reports

Case 1. J. F., a 30-year-old man, was admitted to Cook County Hospital on September 9, 1968 with a history of hematemesis and melena beginning four hours prior to admission. He related a recent heavy alcohol intake but denied previous gastrointestinal bleeding. His bleeding stopped spontaneously, and upper gastrointestinal X-rays were interpreted as normal. The patient was discharged one week later with a presumptive diagnosis of alcoholic gastritis.

The following day he returned, again vomiting blood. On this occasion the bleeding persisted, and during the next four days he received eight units of whole blood. At exploratory laparotomy an edematous, hyperemic, friable gastric mucosa with absent rugal folds was noted. A diagnosis of alcoholic gastritis was presumed, and a vagotomy and pyloroplasty were performed. Postoperatively, bleeding continued and on the second postoperative day air and bile were noted oozing through the wound. At this time the patient admitted that prior to his first admission he had accidentally ingested a large quantity of liquid drain cleaner which contained sulfuric acid.

At reexploration the entire gastric mucosa was found to be gangrenous, with multiple areas of full thickness necrosis. The pyloroplasty had disrupted and was the site of bile leakage. The external surface of the esophagus and duodenum appeared normal. A total gastrectomy, splenectomy, tube duodenostomy, closure of the distal esophagus, feeding jejunostomy and double-barrelled cervical esophagostomy were performed (Fig. 1).

The postoperative course was prolonged and complicated by intraperitoneal abscesses requiring surgical drainage. Seven weeks following the second operation, with the patient's sepsis eradicated and his nutrition maintained via jejunostomy feedings, he was discharged. Prior to discharge, esophagoscopy revealed normal esophageal mucosa without stricture or ulceration.

Three months later, a transabdominal end to side esophagojejunostomy and jejunojejunostomy were performed (Fig. 2). The following month the cervical esophagostomy was closed. At discharge the patient's weight was 108 pounds, whereas, prior to his illness, he weighed 180 pounds.

Eighteen months later the patient was readmitted because of vague postprandial epigastric distress. His weight at that time was 145 pounds. A complete work-up, including an upper gastrointestinal series and esophagoscopy were within normal limits. At followup 2½ years postoperatively, the patient remained asymptomatic.

Case 2. T. M., a 22-year-old woman, was admitted to Cook County Hospital on September 20, 1968, after ingestion of an unknown amount of crystalline lye. Although the patient complained of mild abdominal pain, she had no oropharyngeal burns or abdominal tenderness. On the fourth hospital day the patient suddenly developed severe abdominal pain with signs of peritonitis.

At exploratory laparotomy the entire stomach was found to be necrotic without free perforation. Although the external sur-

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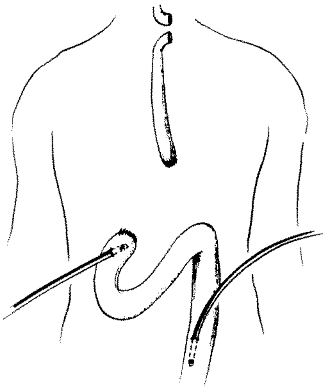

FIG. 1. Schematic drawing of patient J. F., following total gastrectomy and splenectomy. Note the diverting cervical esophagostomy, tube duodenostomy, and feeding jejunostomy.

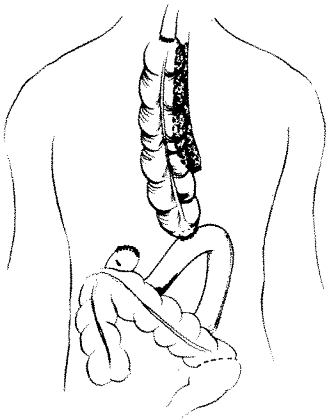

FIG. 3. Schematic drawing of patient T. M., showing a substernal colon bypass, utilizing the descending colon interposed between the cervical esophagus and proximal jejunum. The extensively strictured intrathoracic esophagus has not been removed.

face of the esophagus and duodenum appeared normal, the esophageal mucosa was gangrenous. Because of the patient's precarious condition, extension of the operation to include resection of the esophagus was deemed inadvisable. Consequently, a total gastrectomy, closure of the necrotic distal esophagus, cervical esophagostomy, tube duodenostomy and jejunostomy were performed.

The patient made an uncomplicated recovery and her nutrition was maintained with hyperalimentation and jejunostomy feedings. Three months later a substernal colon bypass procedure was performed utilizing the descending colon interposed between the cervical esophagus and proximal jejunum (Fig. 3).

Postoperatively, a suture line disruption of the proximal esophago-colostomy resulted in a salivary fistula. The patient has subsequently been lost to followup.

Case 3. G. J., a 23-year-old man, ingested an unknown amount of liquid drain cleaner containing sulfuric acid, approximately four hours prior to admission on December 31, 1971. He was seen at another hospital, where gastric lavage was performed prior to transfer to the Cook County Hospital. On admission, he was intoxicated and complained of burning abdominal and substernal pain. He had swollen parched lips and multiple burned areas on the buccal mucosa. There was no abdominal tenderness. Moist rales and rhonchi were auscultated throughout both lung fields.

The patient was managed with intravenous fluids, parenteral antibiotics and nothing by mouth. His chest X-ray revealed bilateral patchy infiltrates, but there was no evidene of free air on either the upright chest or abdominal X-rays. Parenteral steroids were administered as adjunctive therapy for presumed chemical aspiration pneumonitis and a tracheostomy was performed.

Nine days after admission the patient developed abdominal tenderness and signs of peritonitis. At exploratory laparotomy a liter of foul-smelling, bile-stained fluid was found in the peritoneal cavity. The entire stomach and duodenum were necrotic with multiple free perforations, necessitating a total gastrectomy and pancreatoduodenectomy. The distal end of the esophagus was closed and a cervical esophagostomy was constructed. A choledochojejunostomy and feeding jejunostomy were performed and the remaining pancreas was oversewn with separate ligation of the pancreatic duct (Fig. 4). The patient developed progressive pulmonary insufficiency and expired on the second postoperative day.

Case 4. S.W., a 26-year-old male, was admitted to Cook County Hospital on April 4, 1973, after ingesting liquid drain cleaner which contained sulfuric acid. Superficial burns were noted on the patient's tongue and posterior pharynx. Examination of his abdomen revealed minimal left upper quadrant tenderness without evidence of peritonitis.

Six days after admission the patient had several episodes of hematemesis during a 24-hour period; however, blood replacement was not required.

On May 21, 1973, he began vomiting after meals. An upper gastrointestinal X-ray revealed partial stricture of the distal one-third of the esophagus as well as antral stenosis and ulceration (Figs. 5 and 6).

At operation, the distal antral mucosa was observed to be replaced by granulation tissue and a 1 cm ulceration was present on the posterior antral wall. The pre-pyloric region was markedly stenotic, permitting passage of a 3 mm probe (Fig. 7). The operative procedure consisted of a 40% distal gastrectomy with a Billroth I gastroduodenostomy, plus a gastrostomy for subsequent retrograde esophageal dilations.

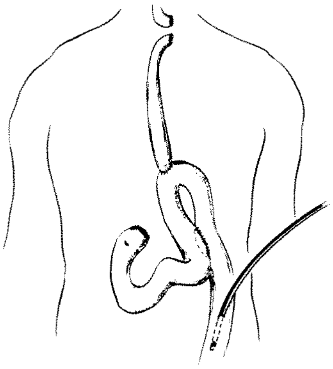

FIG. 2. Schematic drawing of patient J. F., following esophagojejunostomy and jejunojejunostomy. The tube duodenostomy has been removed but the feeding jejunostomy and cervical esophagostomy remain.

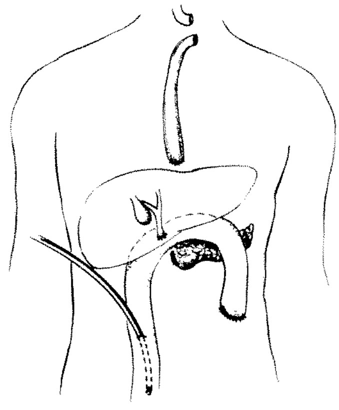

FIG. 4. Schematic drawing of patient G. J., following total gastrectomy and pancreatoduodenectomy. Note the cervical esophagostomy, closure of the proximal jejunum, end to side choledochojejunostomy, and feeding jejunostomy. The resected end of the remaining pancreas has been oversewn.

The patient's postoperative course has been uneventful. He is currently eating without difficulty.

Discussion

Gastric burns often occur following ingestion of corrosive materials, either accidentally by children and alcoholics, or intentionally by emotionally disturbed individuals.

On the basis of experimental animal studies and clinical observation, it is well known that acids tend to destroy the stomach and spare the esophagus.[23] On the other hand, alkalis usually injure the esophagus and spare the stomach.[2] Large amounts of either substance cause severe damage to both organs in approximately 20% of ingestions.[10]

The esophageal sparing noted in acid ingestions appears related to the resistance of the esophageal squamous epithelium to acid erosion and rapid esophageal transit time.[5] Alkalis are usually prevented from damaging the stomach by the neutralizing effect of the acid normally present in the stomach.[24]

In most instances, the gastric burn injury is greatest along the lesser curvature and in the pre-pyloric area.[21] The explanation for this distribution was provided by Testa in 1938. He introduced caustic soda mixed with barium into the esophagus of dogs and demonstrated by X-ray that the alkali-barium bolus flowed along the lesser curvature, produced severe pylorospasm, and was retained in the pre-pyloric area.[23]

The extent of gastric injury appears related to the nature, volume, and concentration of corrosives ingested; the length of time they remain in contact with the stomach; the content of the stomach at the time of ingestion; and the relative tonicity of the pyloric sphincter.[4] At times only superficial mucosal injuries occur which heal uneventfully. More extensive gastric burns which involve the submucosa and muscularis produce various degrees of deformity including antral stenosis,[8,10,12,14,16,19] hourglass strictures,[7,22] and rigidity simulating infiltrating gastric carcinoma.[11,13] Elective surgical correction of these deformities may be necessary when signs of gastric outlet obstruction develop. This usually develops between the first and second month post-injury.[14] Partial gastric resection is the procedure of choice.[7] Gastroenterostomy without resection has been used for definitive therapy, but the uncertain fate of the burned stomach would appear to be a good indication for its resection.[15,18,20] In this regard, O'Donnel in 1949 reported a case of gastric carcinoma developing six years following gastroenterostomy for a nitric acid burn which had produced pyloric obstruction.[17]

In the extensively burned stomach, visceral perforation may occur immediately. More frequently, massive gastrointestinal bleeding or peritonitis are delayed for

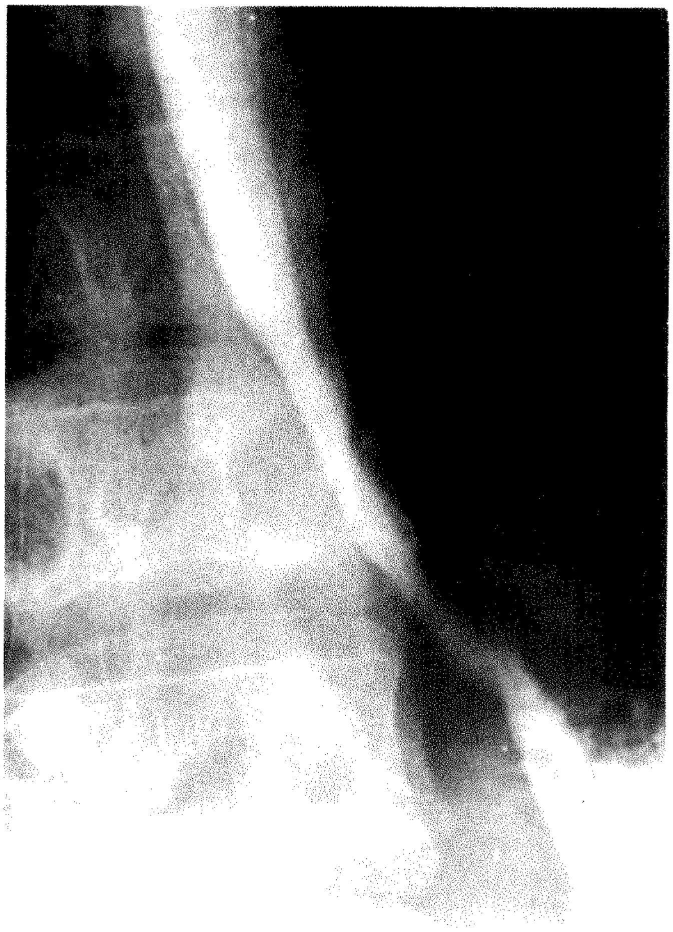

Fig. 5. Barium esophagogram of patient S.W., taken seven weeks following acid ingestion. Note the incomplete stricture of the distal one-third of the esophagus.

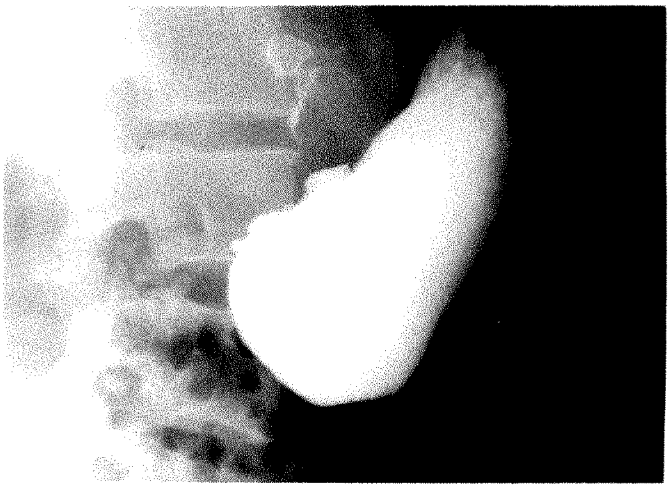

Fig. 6. Barium filled distal stomach of patient S.W., seen on an upper gastrointestinal X-ray performed seven weeks following acid ingestion. The complete antral obstruction and posterior ulcer crater are seen.

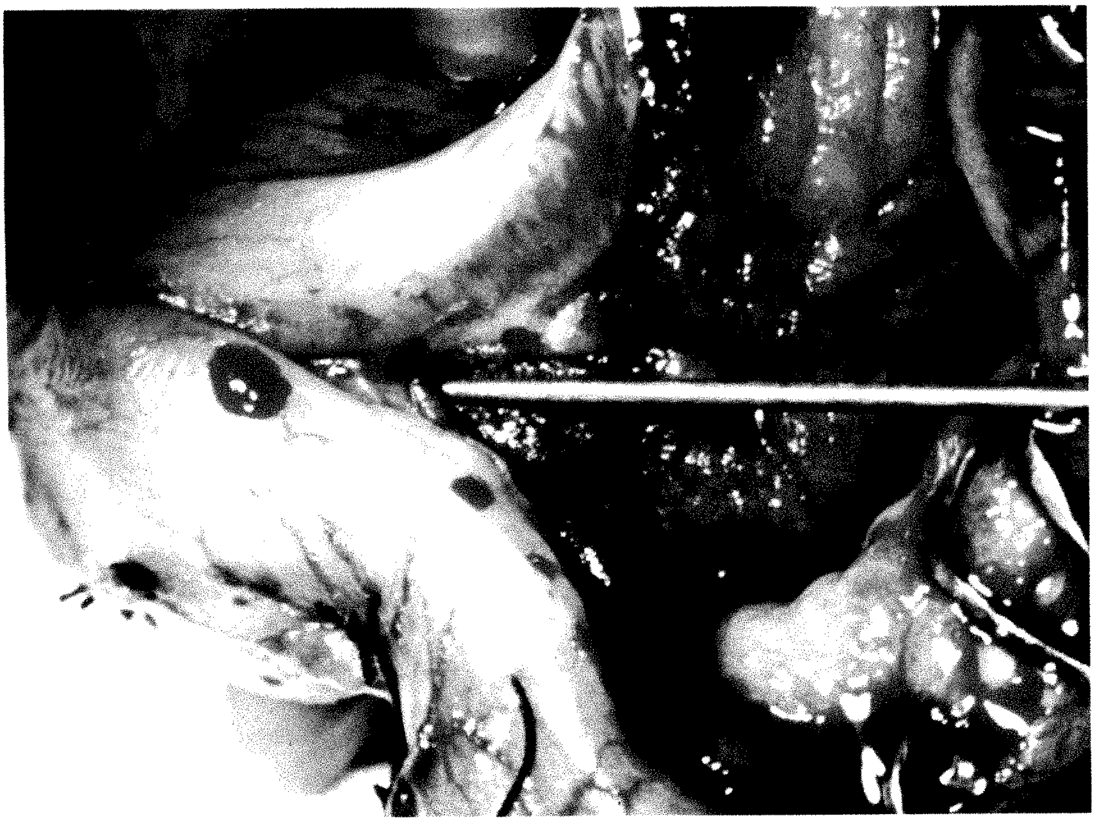

FIG. 7. Intraoperative photograph of the antrum in patient S.W., as seen through a gastrotomy incision. The thickened antral wall as well as the antral stricture, which permits the passage of a 3 mm probe, can be seen.

three to fourteen days, making it imperative that repeated daily abdominal examinations be performed during the first two weeks following corrosive ingestions.[3] The frequent absence of oral and esophageal burns may further mask the suspicion of severe injuries to the stomach and duodenum.

Initial management should consist of nothing by mouth, antacids per nasogastric tube, antibiotics, intravenous fluids, and blood transfusions when indicated.[2,4] Fiberoptic endoscopy should be performed initially to determine the most proximal level of injury.[5] The fiberoptic scope should not be passed beyond the most proximal area of mucosal burn because of the danger of perforation. Developing signs of peritonitis may be masked if steroids are used (Case 3). Gastric lavage or the inducing of emesis is contraindicated, since perforation of the injured organ or tracheobronchial aspiration may occur.

Emergent surgery is indicated for hemorrhage, free perforation or peritonitis. Removal of necrotic tissue is essential and may necessitate total gastrectomy, pancreatoduodenectomy and small bowel resection. Attempts at definitive restoration of intestinal continuity should be deferred at the time of emergency surgery as anastomoses of edematous friable segments of esophagus, stomach or small bowel are prone to disrupt.[3] Following total gastrectomy and closure of the distal esophagus, cervical esophagostomy is recommended for diversion of saliva.[6,9] Tube drainage of the distal esophagus without cervical esophagostomy has been inadequate because esophageal stricture, mediastinitis or tracheoesophageal fistulae have developed.[1] Since the postoperative course may be prolonged, a feeding jejunostomy is nutritionally beneficial and provides either an adjunct or an alternative to intravenous hyperalimentation. Staged reconstruction of intestinal continuity should be performed when the patient's condition warrants.

Full recovery can be expected in most patients and nutrition can be maintained with minor adjustments in eating habits plus supplemental vitamins, especially B_{12}, for patients who have undergone total gastrectomy.

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Arterial Reconstruction with a Modified Collagen Tube:

A Clinical Experience

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Twenty-one modified bovine grafts were implanted in a variety of arterial reconstructions. Successful clinical results were obtained in 60% of the survivors. Attention is directed, however, to the problems of difficulty in reexplorations, the lack of elasticity, and aneurysm development indigenous to the bovine graft. One infection in this series required graft removal and extra-anatomic bypass. The modified bovine graft represents a major advance in vascular reconstruction, but should not be accepted as the ideal arterial prosthesis.

SINCE THE INTRODUCTION of the bovine collagen tube for arterial reconstruction by Rosenberg *et al.*,[9] several groups have corroborated its clinical usefulness. The tube is now readily available, non-antigenic, and handles easily. Patency rates for femoropopliteal reconstruction appear to be at least comparable to those obtained with Dacron prosthesis and in the hands of some workers tend to approach the results obtained with autogenous venous grafts.[5] Aside from the obvious cost factor, our modest experience with the use of the bovine collagen tube in a variety of arterial reconstructions has convinced us that it cannot be considered as the ideal graft and certainly not superior to the venous autograft. This paper reports several drawbacks that we have encountered with bovine grafts that require emphasis before general acceptance for use in primary vascular reconstructions.

Materials and Methods

Twenty-one bovine collagen tubes were implanted in 20 patients. Thirteen femoropopliteal bypasses, bilateral in one case, were constructed for reasons of severe rest pain, trophic lesions of the feet or both. Six patients with major aortoiliac stenosis were subjected to extra-anatomic bypasses, since it was felt that the associated cardiopulmonary disease would increase the risks of a transabdominal approach. In three patients, the femorofemoral cross-over was employed. The axillofemoral route was selected for the other three patients. One of these also had an additional cross-over to the contralateral femoral artery. Two patients each sustained rupture of a popliteal artery from an automobile accident. In both instances, the injury was so extensive that primary repair was not possible. Three and four centimeter segments of bovine collagen tubes were used to bridge the arterial defect as an interposition graft. Bovine graft diameters ranged from seven to ten millimeters. All anastomoses were constructed with either Tevdek or Prolene® cardiovascular suture material. Prior to implantation all of the grafts were thoroughly rinsed in heparinized saline. Complimentary procedures included endarterectomy, profundoplasty and sympathectomy. The followup period has been from three months to two years.

Results

Table 1 is a summary of the results obtained following these 21 bovine implants in twenty patients. Three patients (15%) succumbed within the first week of surgery of associated coronary artery or cerebrovascular occlusive disease. One of these patients had undergone axillofemoral bypass and the graft was noted to be closed shortly before death. In the other two patients, both with femoropopliteal bypasses, the grafts remained patent until the demise of the patients. Of the remaining

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TABLE 1. *Bovine Graft Study*

Graft Type	Number	Success	Modified Success	Early Failure (<2 weeks)	Late Failure (>2 weeks)	Early Mortality (<1 week)
Femoropopliteal	11	2	2*	3‡	2*	2
Femorotibial	1	1				
Femoroperoneal (composite with vein)	1		1†			
Popliteal interposition	2	1		1*		
Femorofemoral	3	3				
Axillofemoral	3		1*		1*	1
Total	21	7	4	4	3	3

* Following thrombectomy
† Following aneurysmectomy
‡ Infection (1), thrombosis (2)

17 patients, 11 (61.1%) achieved a successful clinical result with graft patency by subjective and objective criteria. Of these, seven (38.9%) had perfectly uncomplicated postoperative courses. Three of these seven had femoropopliteal bypasses, one of which crossed the knee. Three had femorofemoral bypasses, and one had a popliteal interposition. The other four successful cases (22.2%) did, however, develop some complication. Two femoropopliteal grafts thrombosed, one at 48 hours and the other at three weeks after implantation. Both were successfully reopened by prompt thrombectomy. An axillofemoral graft thrombosed at 4 weeks, was successfully thrombectomized, closed again in another 4 weeks, and was successfully reopened again. The gangrenous ulcers of the feet healed and remained so. The other complication managed successfully was a false aneurysm in a femoroperoneal bypass that appeared 4 weeks after the original surgery at the suture line of the bovine-autogenous vein composite anastomosis. The defect was repaired by a Dacron patch angioplasty.

Seven failures (38.9%) occurred; four of these (22.2%) occurred within two weeks after operation. The remaining three failures (16.7%) occurred more than two weeks following graft implantation.

Histologic evaluation of removed graft segments showed retention of the original collagen fibers. Invading host collagen was noted with the increasing age of the specimens. The outer edge of the graft thus became progressively indistinct. An early inflammatory reaction consisting of polymorphonuclear leukocytes was also noted in early specimens with minimal reaction later aside from the desmoplastic response. One biopsy specimen, taken at four weeks, showed thinning of the wall and focal hyalinization.

Discussion

Our experience with the modified bovine collagen tube for a variety of arterial reconstructions supports the data previously presented by Dale,[2] Keshishian,[5,6] Rosenberg,[7] and Rosenberg[8] with respect to clinical usefulness and patency rates. However, several deficiencies in the use of this new graft have become obvious and we believe should be properly emphasized prior to any general acceptance of the graft by vascular surgeons.

Difficulty in Reexplorations

The major drawback in our use of the bovine collagen tube was the difficulty encountered in dissecting out the graft when reexploration was required. When thrombectomy was indicated as early as three weeks after graft implantation, tedious time-consuming dissection was necessary to avoid entering the graft substance itself. Fibrous reaction was usually so intense that the proper cleavage plane was almost obliterated. Additionally, the graft itself was very fragile and extreme care was required in placing additional sutures. Sufficient graft length must be obtained prior to arteriorrhaphy to avoid even the slightest tension on the anastomosis and the pulling out of the sutures. Though thrombectomy was satisfactorily concluded in all instances, we feel that the difficulty encountered in reexploring the graft weighs against its routine use in clinical practice.

Lack of Elasticity

The lack of elasticity can be easily compensated for by accurate assessment of the length of graft required. However, we have noted a tendency for kinking to occur at anastomotic areas unless a minimal curve is created at the origin or termination of the graft. Keshishian[5] demonstrated "wrinkling" or "accordioning" of grafts crossing the knee joint in the hyperflexed position. Though patients are instructed to avoid positions of extreme flexion, such as squatting, one of our low femoral popliteal implants failed in a patient who slept with his knees sharply flexed.

False Aneurysm

The two false aneurysms that occurred in this series were in the popliteal region in complicated femoropopliteal reconstructions. In the first case, groin wound infection ultimately required extraanatomic transobturator iliopopliteal bypass using a Dacron prosthesis and removal of most of the heterograft. The false aneurysm occurred in the distal two to three centimeter segment of heterograft that had been left anastomosed to the popliteal artery. It appeared four weeks after the distal cuff had been oversewn. It was not possible to delineate a discrete origin in the body of the graft or either of its suture lines. Cultures of the specimen failed to produce any growth.

In the second case a false aneurysm appeared in the popliteal region at the site of the bovine-autogenous vein composite anastomosis for a femoroperoneal arterial bypass. The aneurysm was also noted four weeks after arterial reconstruction. At surgery, the defect was found on the bovine side of the composite anastomosis and was successfully repaired with a knitted Dacron velour patch.

Both of these false aneurysms occurred adjacent to suture lines. It is not possible to delineate the role of the graft apart from infection in the first case, nor the role of the graft from technique in the second case. Dale[1] reported one aneurysm in 32 clinical patients that required graft replacement. Dillon and Postlethwait[3] resected eight graft aneurysms in a group of 38 bovine grafts implanted from 1962 to 1971.

It is apparent that success or failure of a vascular reconstruction is not only dependent on a given set of variables such as runoff, type of graft or technical factors, but also on the evolution or stability of the disease process itself. A late graft closure is not necessarily a failure of the graft. Intelligent evaluation of isolated facets of a vascular reconstruction can only be made with continued accumulation of the data in many long-term clinical cases. In the two femoropopliteal bypass grafts that failed late, clear angiographic evidence of progressive obliterative disease in the runoff circulation was obtained by intraoperative angiography. Additionally, duing thrombectomy of the proximal graft area, hyperplastic tissue as described by Imperato et al[4] was removed from the femoral artery. Diminished inflow and outflow were undoubtedly responsible for failure in both instances. The use of the bovine heterografts may not have contributed to these failures.

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Maintenance of Viable Segments of Human Artery in Vitro

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A system for maintaining viable segments of atherosclerotic human artery *in vitro* for periods of up to 32 days is described. Viability of the segment has been confirmed from study of lactate metabolism and vessel wall histology. Preliminary lipid studies using TLC on plasma perfusate indicate lipid may be removed from the vessel wall during perfusion.

A SYSTEM HAS BEEN DEVELOPED for maintaining viable segments of atherosclerotic human artery *in vitro* for four weeks. The present report describes the system and documents vessel viability with both metabolic and histologic data.

System

The system consists of a constant perfusion apparatus with a small built-in membrane oxygenator (Fig. 1). The pertinent components of the system include:

1. Oxygenating Chamber (Fig. 1). This funnel-shaped, glass chamber fits within the perfusion chamber. The upper end of the chamber is capped with a rubber cork through which passes an oxygen inflow needle, an oxygen outflow needle and the perfusion inflow. Fifteen feet of silicon rubber capillary tubing (I.D. 0.012 inches P.D. 0.025 inches)* are attached at either end to the oxygen inflow and outflow needles and randomly folded into the oxygenating chamber. Care must be taken in placing the tubing to avoid kinking. The perfusate enters through the perfusion inflow, dumps into the oxygenating chamber and exits through an outflow port. Over this outflow port, a segment of vessel is tied, the perfusate passes through this and out the other end of the vessel where it collects in the perfusion chamber. It is drained from here via polyethylene tubing which passes through a constant perfusion roller pump and back into the perfusion inlet.

2. Perfusion Chamber. This chamber collects the perfusate, bathes the outer wall of the vessel segment and contains, in its upper end, the oxygenating chamber.

3. Temperature control in the range of 90–98 F is maintained with an infrared lamp and adjusted by altering lamp distance. A dummy perfusion system with an implanted thermometer monitors the perfusate temperature.

4. Perfusate. Two perfusates have been tested: (a) 10% foetal calf serum in Eagle's Media with 10 cc L-glutamine per 1000 cc perfusate; and (b) Whole human plasma which has been stored at 4 C for approximately 14 days.

Antibiotics are added to the perfusate as follows (doses given per 1000 cc perfusate):

Amphotericin B 250 mgm
Potassium Penicillin G 1.25 × 10^7 n
Mycifradin Sulfate (Neomycin) 12.5 gm
Bacitracin 25,000 n
Streptomycin 12.5 gm

Method of Study

A segment of atherosclerotic human artery is harvested from a cadaver less than 12 hours after death. The vessel is taken under sterile condition. A thin slice of the distal vessel margin is taken and fixed in Formalin for imbedding, sectioning and H & E staining. The vessel is tied to the oxygenator outflow nipple and inserted into the perfusion chamber. The entire system is then primed

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* Dow Corning 602-105.

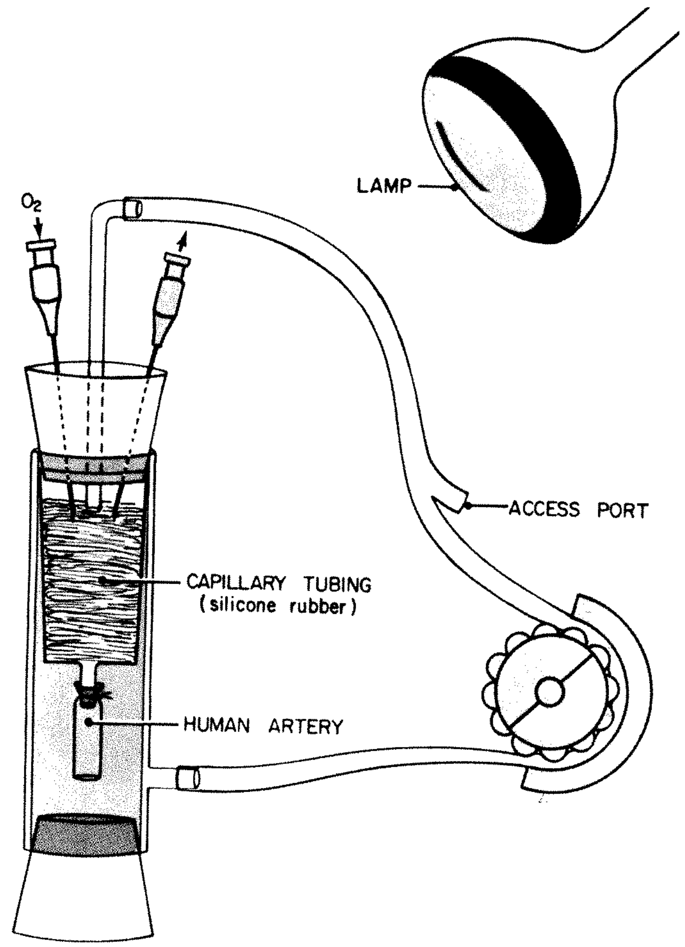

FIG. 1. Diagram showing continuous perfusion cycle from roller pump into the oxygenating chamber out through the vessel into the collecting reservoir and out of there to the pump.

with perfusate, the perfusion began and temperature regulated.

The perfusate is changed at 3-day intervals. pH is checked daily and maintained between 7–30 and 7–50 by addition of $NaHCO_3$ Lactate levels and thin layer chromatography (TLC) were performed on the perfusate before and after a 3-day exchange once each week in five plasma perfusions and three Eagle's Media perfusions. Sections of the vessel are taken once each week for H & E staining and histologic examination

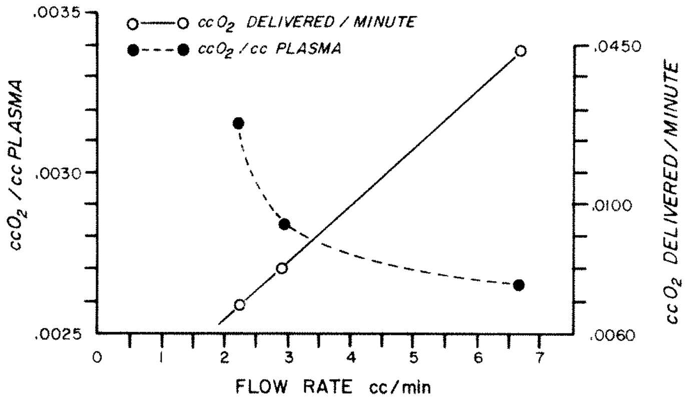

FIG. 2. Graphic relationship of perfusate flow to total oxygen delivered per minute and oxygen delivered per cc of plasma.

TABLE 1. *Perfusate Lactate Levels**

Day	Plasma Perfusate Lactate mgm%	Eagle's Media Perfusate Lactate mgm%
0	18.8 (5)†	20 (3)†
7	39.1	10
14	31.0	9.5
21	45.2	—
28	53.3	—

* Perfusate changed every 3 days.
† Numbers in parentheses indicate number of samples studied.

Results

The oxygenation has proved quite efficient within the ranges of flow rate utilized in this system (Fig. 2). Six-

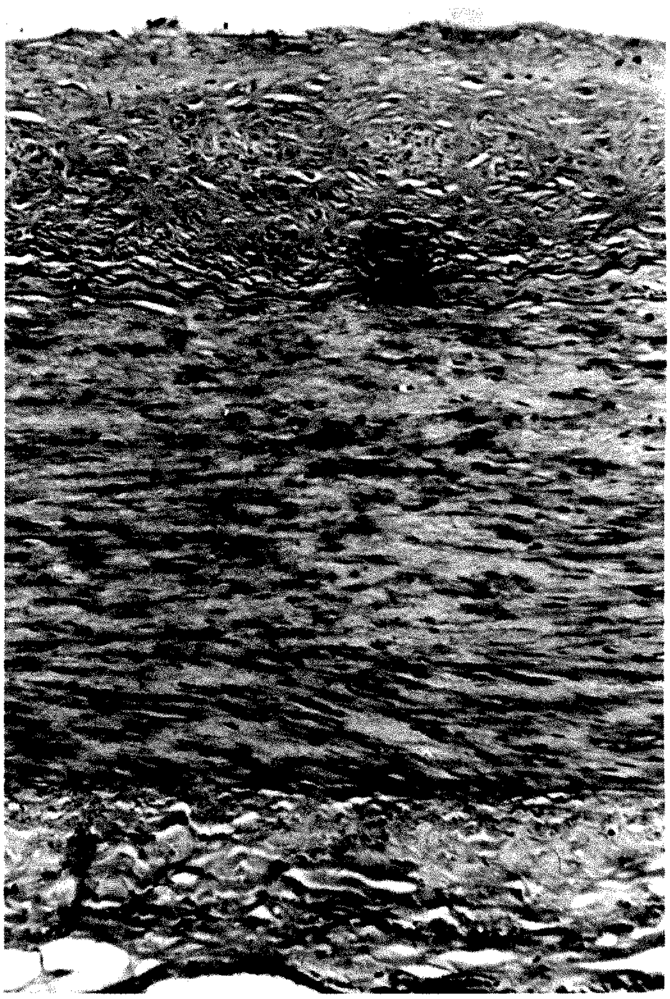

FIG. 3. Fresh autopsy specimen of vessel 5½ hours after death. Cellular and vessel wall architecture appears intact (×250).

teen vessels have been maintained for periods of from 14 to 32 days. Lactate production is seen with Eagle's Media perfusate and with plasma perfusate (Table 1). Microscopically, cellular integrity is maintained, basement membrane remains intact and the configuration of the vessel wall remains unaltered (Figs. 3 and 4). The time limiting factor is the onset of fungal infection of the vessel wall. This results in rapid loss of cellular structure in the vessel wall and obvious invasion of the tissue with micelial forms (Fig. 5).

TLC on Eagle's Media perfusate demonstrates no apparent change in lipid composition of the perfusate (Fig. 6). Using plsama perfusate, the presence of a yet unidentified lipid fraction which migrates slightly faster than our triglyceride controls has been consistently noted using TLC (Figs. 7a and 7b).

Discussion

A system for maintaining a segment of viable human artery for periods of up to 32 days is described. Evidence of lactate utilization and production confirms the metabolic capability of the vessel wall. Histologic sections further confirm the vessel wall viability.

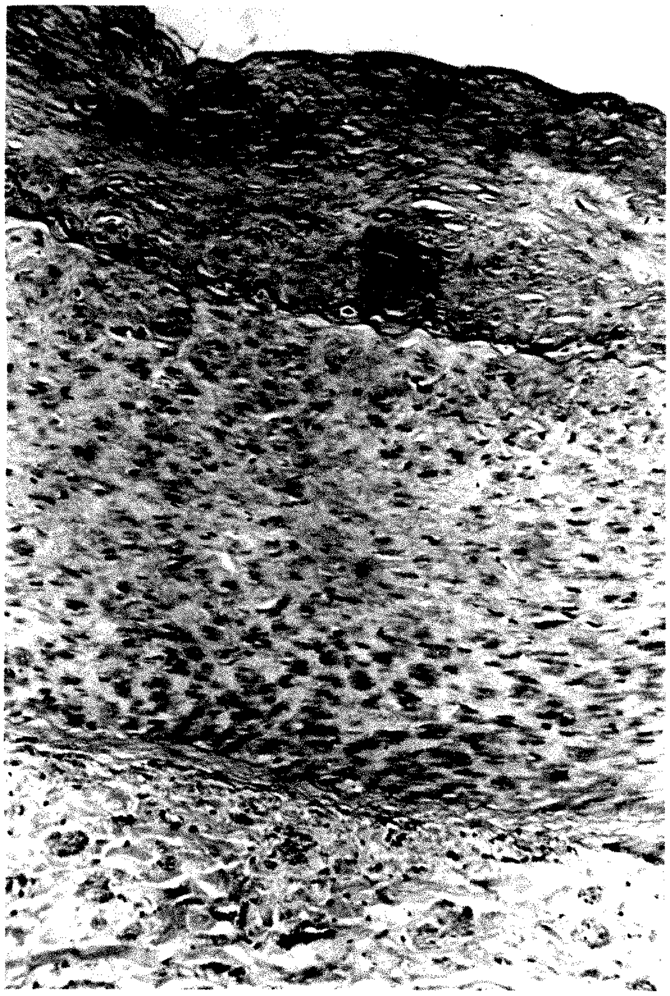

FIG. 4. Section from same vessel after 23 days of perfusion. Both cellular integrity and vessel wall architecture are preserved indicating continued viability (×250).

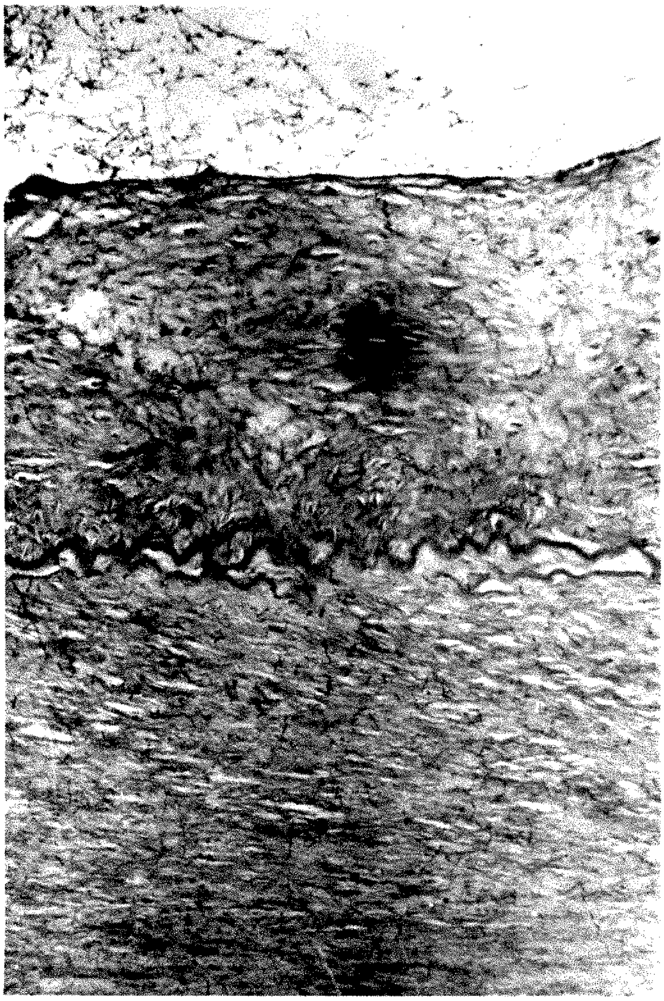

FIG. 5. Section from same vessel showing fungal infection of vessel wall and perfusate. Cellular integrity is lost, no nuclei are seen and dissolution of vessel architecture is evident in all layers. Note thickening and indistinct margins of basement membrane (×250).

Fungal overgrowth invariably occurs and limits the duration of vessel viability in the system. Previous work with this system using only Penicillin and Streptomycin in the perfusate has shown fungal overgrowth to occur as early as a week and not later than 10 days. The current antibiotic regimen, combined with strict aseptic management of the system has extended this to as long as 32 days.

An absence of any lipid transport has been demonstrated using Eagle's Media—10% foetal calf serum as perfusate. Using human plasma stored at 4 C lipid transport out of the vessel wall is suggested by preliminary work using thin layer chromatography. Lipoproteins are essential to lipid transport in plasma and their presence in the plasma perfusate may explain the

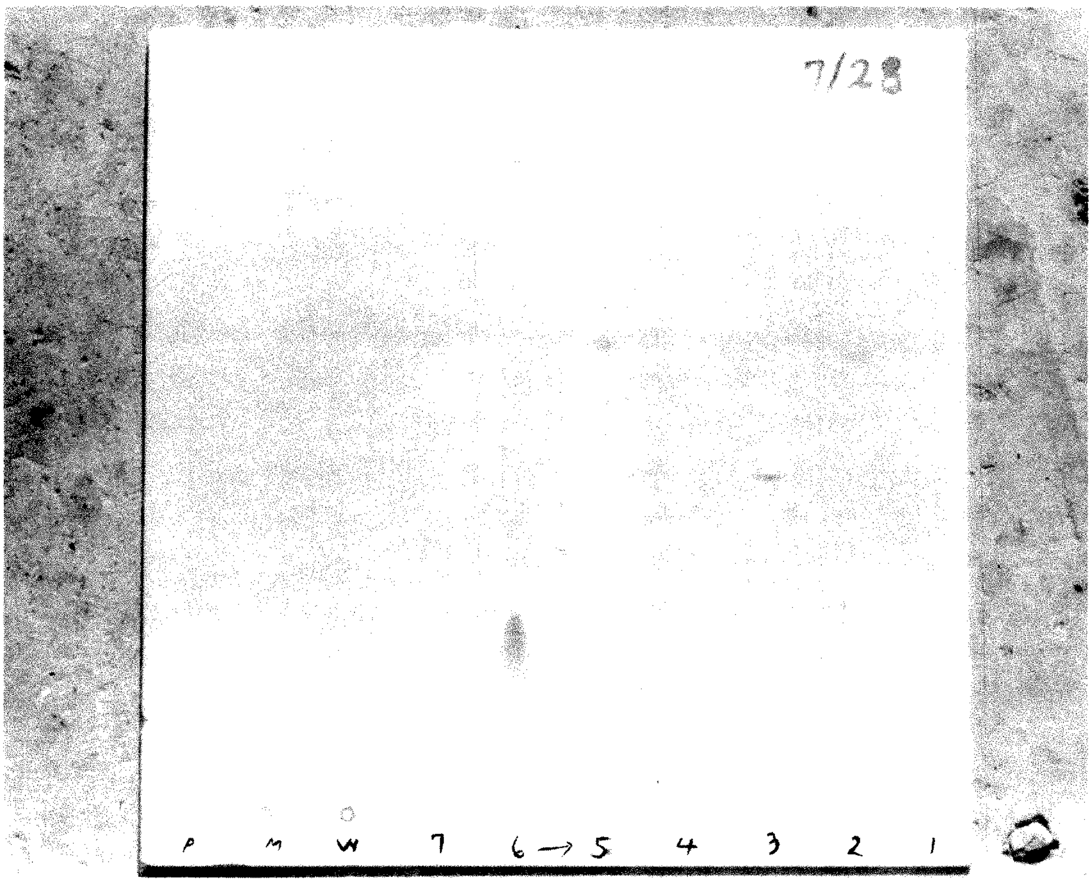

FIG. 6. Thin layer chromatography shows no evident lipid content in the perfusate (three spots on the left) using Eagle's Medium and 10% foetal calf serum as a perfusate.

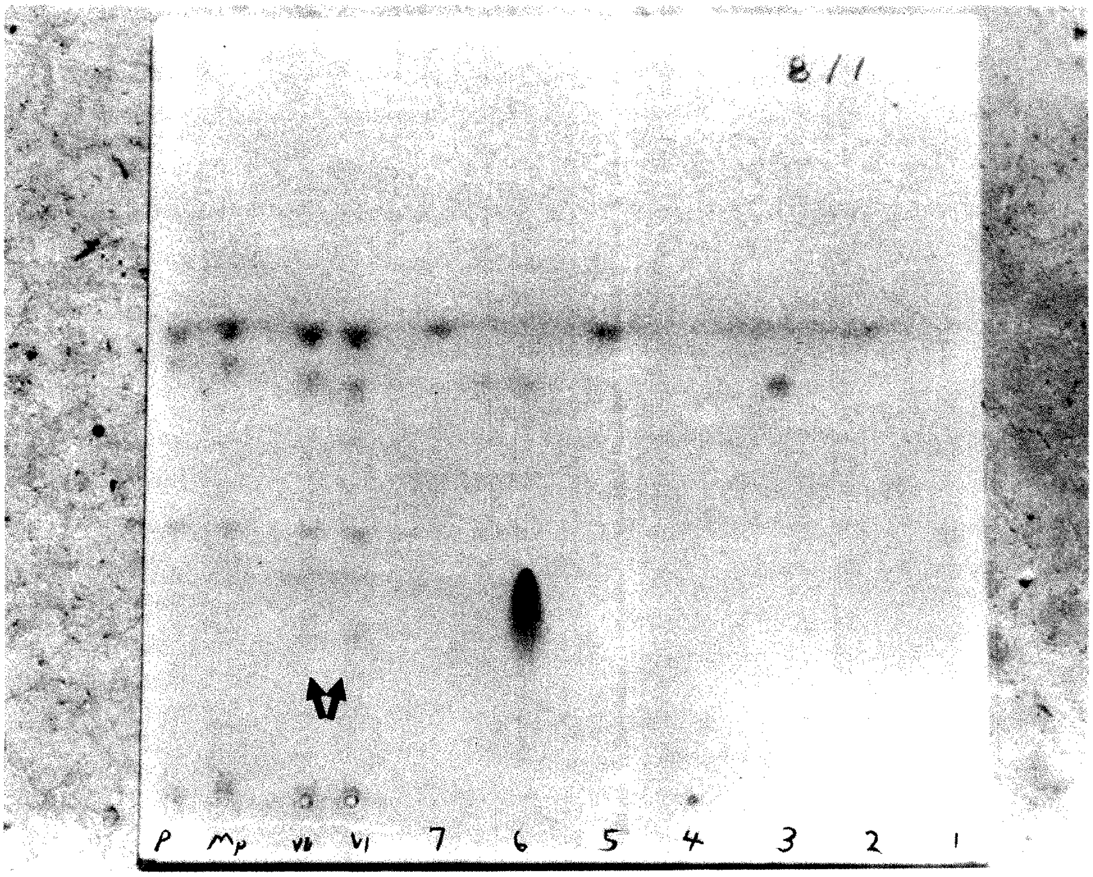

FIG. 7a. Plasma perfusate shows considerable lipid TLC. Perfusate from vessels VI and VII demonstrated a lipid fraction (arrows) not found in plain plasma (P) and plasma with antibiotics (MP).

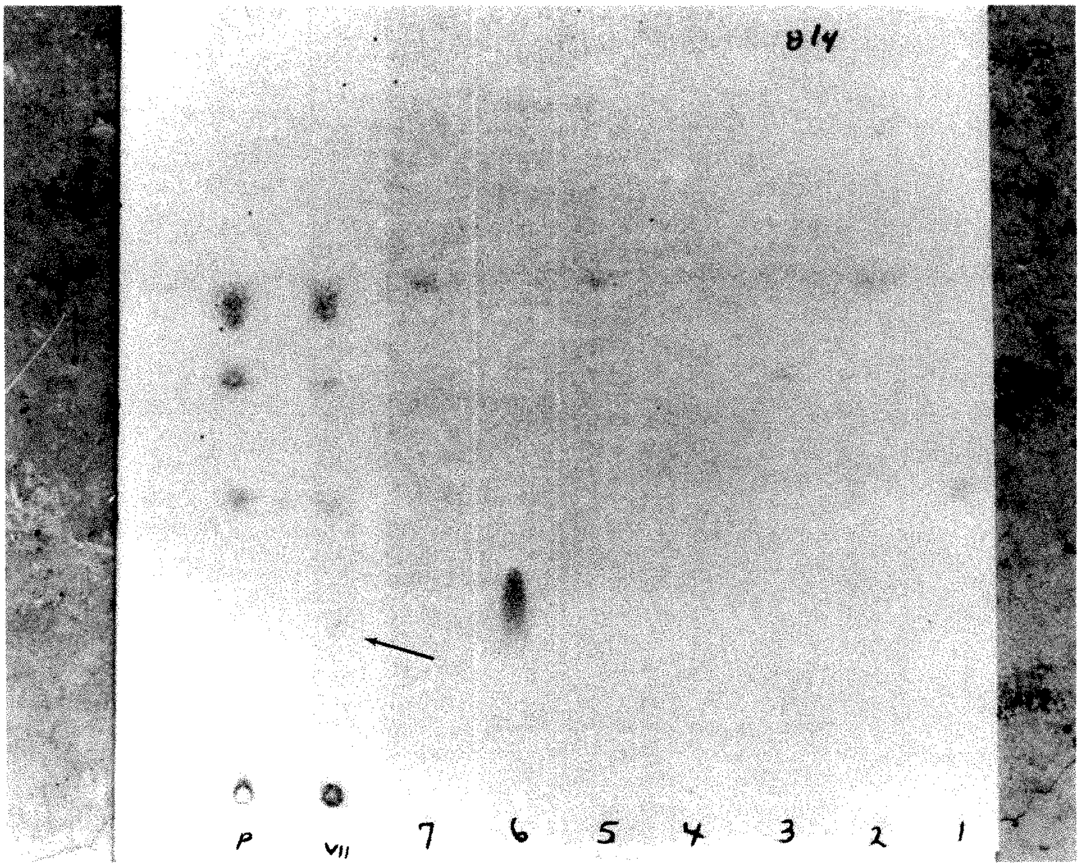

FIG. 7b. Another plasma perfusate showed similar unidentified lipid in perfusates after 3 to 4 days of vessel perfusion (arrow).

apparent elution of lipid from the atherosclerotic vessel segment. This remains highly speculative, however, as lipoproteins, particularly B lipoprotein are known to be labile and to disappear rapidly from plasma stored at room temperature. Use of fresh human plasma as perfusate and more sophisticated lipid analysis of the perfusate are currently underway to more adequately define this observation.

Splenic Vein Thrombosis with Oesophageal Varices:

A Late Complication of Umbilical Vein Catheterization

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On the basis of observations made on three infants, a description is given of a late complication of umbilical vein catheterization not hitherto reported. The children showed the symptoms of thrombosis of the splenic vein with secondary splenomegaly and marked gastric and/or esophageal varices, while the portal vein showed no abnormality. The diagnosis was preoperatively established by means of selective angiography of the superior mesenteric artery and the splenic artery. Treatment in these three cases consisted of splenectomy, with good clinical and radiological results.

THE CAUSE OF ESOPHAGEAL VARICES is usually found in excessively high pressure within the venaportal system as a result of intrahepatic or extrahepatic obstruction in this system.

However, esophageal varices can also develop in the presence of an entirely patent portal vein, if the efferent flow through the splenic vein is obstructed while the supply through the splenic artery remains normal. This results in congestion in the spleen, which must drain itself of its blood through collateral veins. The consequence is an enlargement of the spleen and varicose dilatation of the veins between the spleen and the stomach with, in a later stage, dilatation of the veins in the cardia and the esophagus as well. Ultimately this leads to the classical features of (possibly bleeding) esophageal varices (Fig. 1).

Thrombosis of the splenic vein is a rare abnormality. In children, such an obstruction of the splenic vein may possibly be due to the use of an umbilical vein catheter. There are reports on complications of umbilical vein catheterization such as perforation of the vascular wall, thrombosis of the portal vein, liver infarction, pulmonary embolism and colon perforation.[1,6,8–11]

The possibility of a relationship between isolated thrombosis of the splenic vein with esophageal varices and the use of an umbilical catheter immediately after birth, can be illustrated by the case histories of three patients whom we treated in June and July 1973.

Case Reports

Patient A was a girl born on November 22, 1970 after a pregnancy of 31 weeks; birth weight 1400 g. After birth she was given a 10% glucose solution through an umbilical vein catheter which was removed after 72 hours. The position of the catheter was not radiologically controlled.

After a followup period of 6 months during which development was uneventful, she was discharged from the hospital.

About two years later, on April 17, 1973, she was admitted to the Diaconessen Ziekenhuis, Groningen with anemia (hemoglobin 7.7 g/100 ml; hematocrit 21), hematemesis and splenomegaly. X-rays of the stomach disclosed filling defects in the fundus. After an abundant intestinal hemorrhage, exploratory laparotomy revealed a normal liver and a greatly enlarged spleen; markedly dilated veins were observed against the posterior abdominal wall, in the splenocolic ligament and around the fundus of the stomach. A biopsy specimen from the liver was normal. The possibility of portal vein thrombosis with hemorrhage from gastric or esophageal varices was considered. No further surgical treatment was carried out. The bleeding ceased spontaneously. The postoperative radiograph of the esophagus revealed extensive varices (Fig. 1).

On June 4, 1973 the child was admitted to the Groningen University Hospital for further diagnostic work.

The aortogram showed no abnormality. Selective angiography of the superior mesenteric artery was likewise negative, and during the venous phase the efferent flow through the portal vein was seen to be adequate. The selective angiogram of the splenic artery showed no abnormality of the artery itself but re-

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vealed marked splenomegaly. In the venous phase of this selective angiogram a complete stop was observed in the splenic vein, immediately central to the entry of the vena coronatia gastrica. The contrast medium was drained off through this vein and through varicose veins along the gastric fundus, cardia and esophagus.

In view of this finding, splenectomy was performed on June 9, 1973 in an effort to abolish the pressure in the varicose collateral system. In view of the risk of bleeding from the varices, the splenic vein in the upper edge of the pancreas was not dissected free in a central direction, and the site of obstruction was therefore not brought into view. The spleen weighed 80 g. The histological diagnosis was splenomegaly.

The postoperative course was uneventful. The child received prophylactic antibiotic medication.

Followup radiography of the esophagus on July 25, 1973 (more than six weeks after the operation) revealed unmistakable regression of the esophageal varices, even though they had not yet disappeared completely.

Patient B was a boy born on 10th April 1967 after a pregnancy of 31 weeks; birth weight 1200 g. After birth he was given a 10% glucose solution through an umbilical vein catheter. The period during which this remained *in situ* is unknown. The child developed uneventfully. Routine followup, however, revealed gradual enlargement of the spleen. Blood morphology and chemistry were normal. Scanning disclosed a small liver and a greatly enlarged spleen. Radiographs of the long bones showed juvenile bone cysts; a diagnosis confirmed by biopsy. Radiographs of the stomach and the esophagus showed unmistakable varicose filling defects.

The aortogram showed no abnormality. Selective angiography of the superior mesenteric artery was likewise negative; during the venous phase the efferent flow through the portal vein was seen to be adequate. The selective angiogram of the splenic artery showed that this artery was patent, but the splenic vein failed to fill. The greatly enlarged spleen drained itself through varicose veins along the stomach and the esophagus.

In view of this finding, splenectomy was performed on July 2, 1972 in an effort to abolish the pressure on the varicose veins. The spleen weighed 300 g and showed marked local fibrosis. At the site of the hilus the splenic vein was patent, but at a more central level it was obliterated. Extensive varices were present along the stomach and the left dorsolateral abdominal wall.

The postoperative course was complicated by a protracted subfebrile temperature, which disappeared spontaneously. The boy was considered too old for prophylactic antibiotic medication.

Followup radiography of the esophagus on August 8, 1973 (5 weeks after the operation) showed unmistakable regression of the esophageal varices, and normal plication of the esophageal mucosa began to be visible again.

Patient C was a boy born on August 16, 1972 after a pregnancy of 34 weeks; birth weight 1750 g. In view of hypoglycaemia he was given a 10% glucose solution through an umbilical vein catheter during 24 hours after birth. The position of the catheter was not radiologically controlled. The child's development was uneventful, and after 6 weeks he was discharged from hospital. Gradual enlargement of the spleen was observed in the course of the followup. Blood morphology and chemistry were infectious mononucleosis were negative. Esophageal radiographs showed no varices. Urinalysis and IVP were negative. After hospitalization for further investigation the child's hemoglobin concentration fell to 8.8 mg/100 ml; the leucocyte count fell to 1600/mm^3 and the platelet count to 90,000/mm^3. The bone marrow punctate was normal. On June 26, 1973 he was admitted to the Groningen University Hospital.

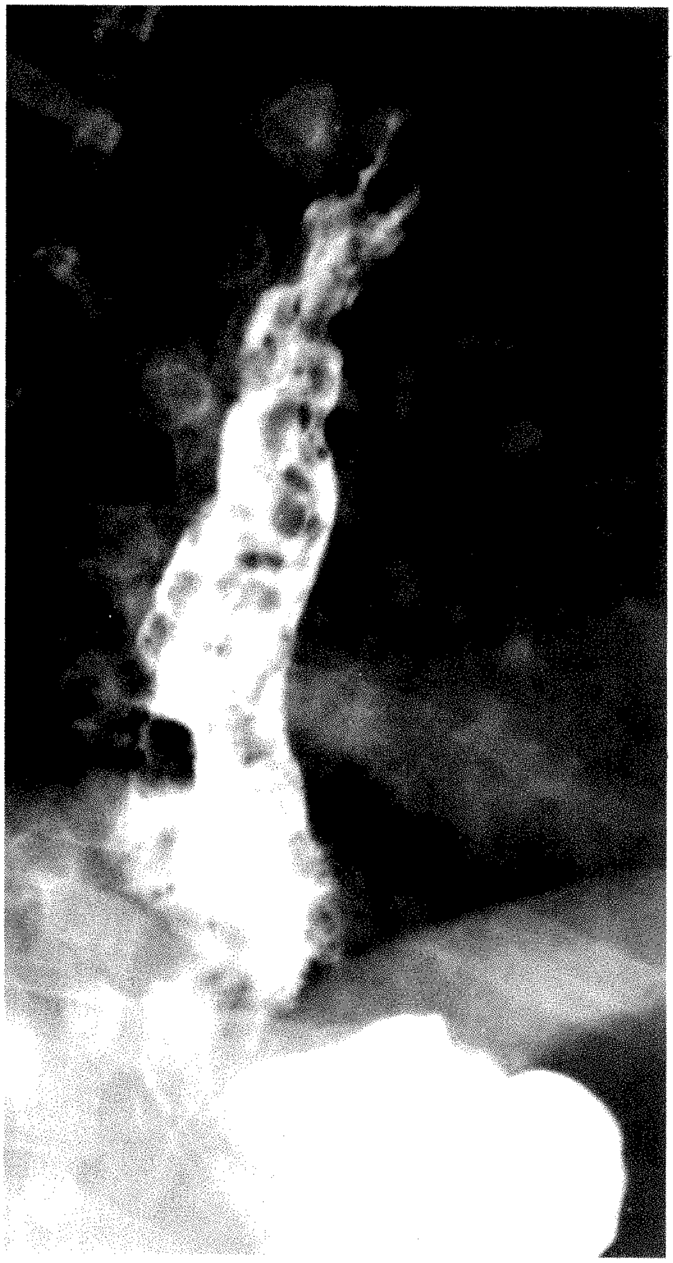

FIG. 1. Unmistakable filling defects in the esophageal radiograph, caused by esophageal varices in a 30-month-old girl with splenic vein thrombosis resulting from umbilical vein catheterization.

The aortogram showed no abnormality. Selective angiography of the superior mesenteric artery likewise failed to show any abnormality; during the venous phase an adequate efferent flow through the portal vein was seen (Figs. 2 and 3). Selective angiography of the splenic artery showed that this was also normal, but during the venous phase a stop was visible in the splenic vein immediately central to the entry of the vena coronaria gastrica (Figs. 4–6). The congested spleen drained itself through varicose veins along the fundus of the stomach.

On the basis of this finding, splenectomy was performed on July 16, 1973, in an effort to abolish the high pressure in the collateral venous system. Extensive varices were found along the

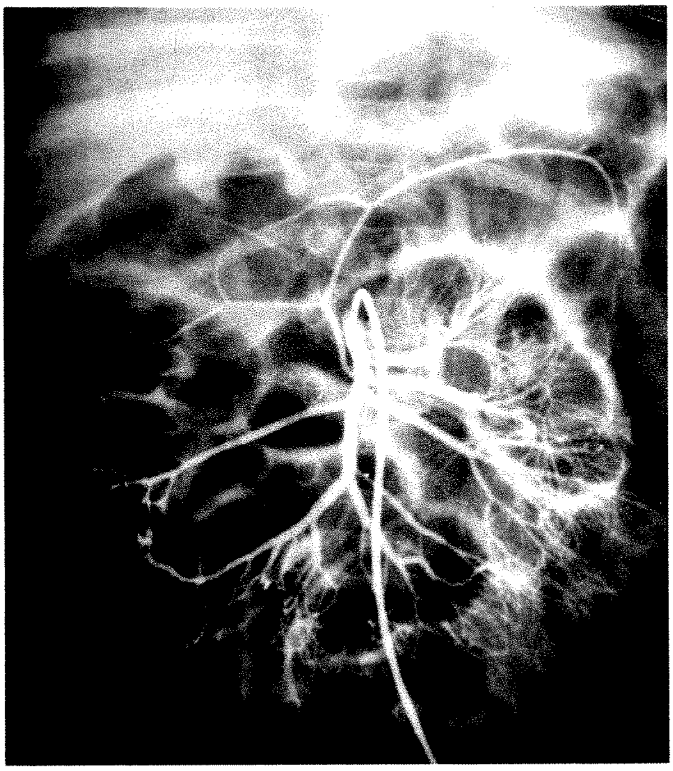

FIG. 2. Normal arterial vascular pattern in selective angiogram of the superior mesenteric artery in an 11-month-old boy with splenic vein thrombosis resulting from umbilical vein catheterization.

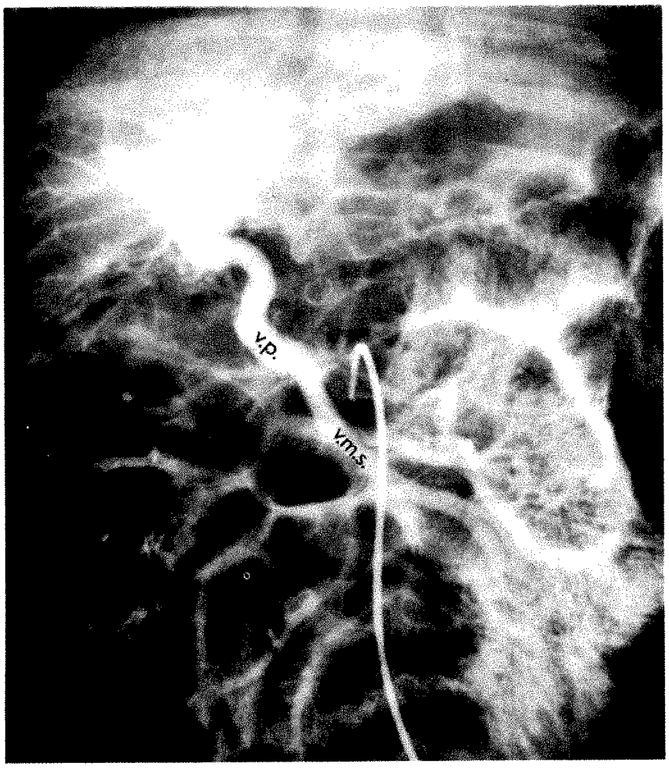

FIG. 3. The venous phase of the selective mesenteric angiogram of Fig. 2 shows adequate efferent flow through the portal vein. (v.p. = vena portae, v.m.s. = vena mesenterica superior.)

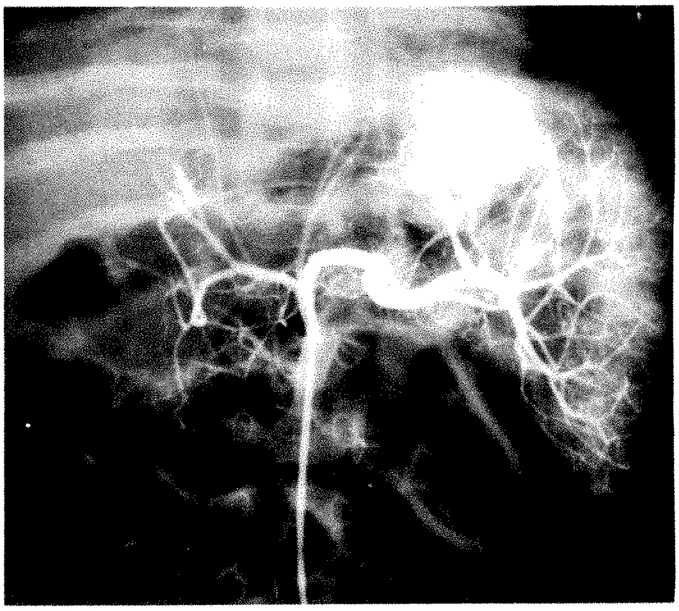

FIG. 4. Selective angiogram of the splenic artery of the same patient (Figs. 2 and 3). Normal splenic artery. Enlarged spleen.

stomach and the posterior abdominal wall. In view of the hemorrhagic risk, the splenic vein was not dissected free from the pancreatic edge, and the site of the venous stop was therefore not brought into view. The spleen weighed 105 g and at histological examination showed the features of chronic congestion with unmistakable diffuse fibrosis. The postoperative course was uneventful. The patient was given a prophylactic maintenance dose of antibiotics until he reaches age 5.

These three children were prematures (31 weeks/1400 g; 31 weeks/1200 g; 34 weeks/1750 g), who as neonates received a 10%

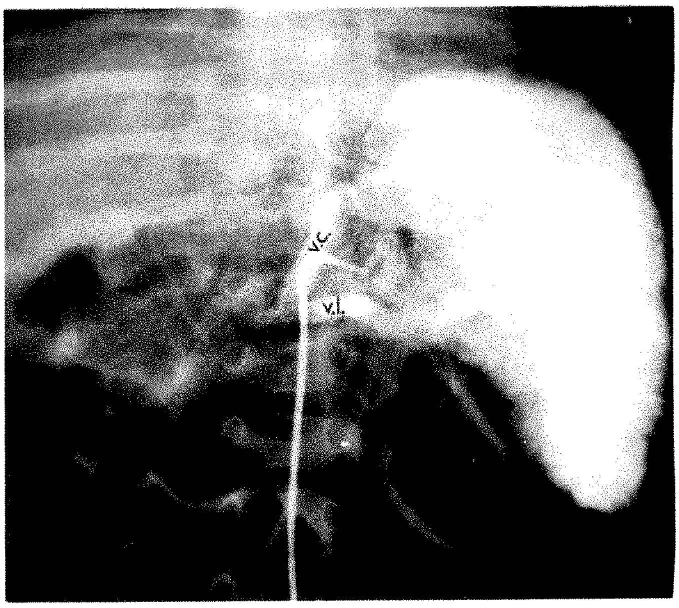

FIG. 5. The venous phase of the selective splenic artery angiogram of Fig. 4 shows an unmistakable stop in the splenic vein; efferent flow through collaterals along the fundus of the stomach. (v.l. = vena lienalis. v.c. = vena coronaria gastrica.)

glucose solution through an umbilical vein catheter. All three gradually developed splenomegaly with varices of the stomach and/or esophagus which were slight in the youngest child (patient C, aged 11 months), but already very severe in the two older children (patients A and B, aged 30 months and 6 years, respectively).

By means of selective angiography of the mesenteric and splenic artery, a patent portal vein and an obstructed splenic vein were demonstrated in these children, in whom the blood from the congested spleen was drained through varicose gastric and/or esophageal veins. Treatment consisted of splenctomy in these three cases, and with good results.

It is justifiable to postulate a relationship between the umbilical vein catheterization and the development of splenic vein thrombosis with esophageal varices in these three cases. So far as we could establish from the literature, this complication of umbilical vein catheterization has not been previously described.

Discussion

The umbilical vein is localized in the free edge of the falciform ligament, and opens up into the left half of the portal sinus (Fig. 7). Opposite its point of entry the ductus venosus arises from the portal sinus. The ductus venosus empties into the left hepatic vein immediately before the latter opens up into the inferior vena cava. Experiments by Soeters[7] on neonatal cadavers in which he catheterized the umbilical vein under radiological control showed that it was sometimes difficult to cannulate the ductus venosus. In these cases the catheter deviated to the left or the right branch of the portal vein.

Anyone who has ever catheterized an umbilical vein under fluoroscopic control, knows how readily the catheter deviates to the left and enters the splenic vein. In the absence of fluoroscopic control there is a ready risk that a solution is infused into the splenic vein through such an ill-placed catheter.

This creates a situation which is virtually ideal for the development of splenic vein thrombosis. The catheter invariably causes slight-to-severe traumatic intimal lesions,” And the fluid infused (e.g. a 10% glucose solution) may produce an additional chemical intimal lesion.[9]

A factor which may play an important additional role in the etiology of the intimal lesion is an infection introduced via the catheter. In umbilical artery catheterization, this factor seems of less marked importance.[3] As a result of the intimal lesions, swelling and degranulation of blood platelets give rise to the release of adenosine diphosphate (ADP). The ADP in turn promotes platelet aggregation. In normal situations this process abolished by a rapid flow of blood, but this cleansing mechanism is rendered less effective by the presence of a catheter which is relatively thick as compared with the lumen of the splenic vein (particularly in prematures). Spasm of the vein in response to the intimal irritation further reduces the blood flow rate. And we know that stasis is an important factor in the aetiology of thrombosis.

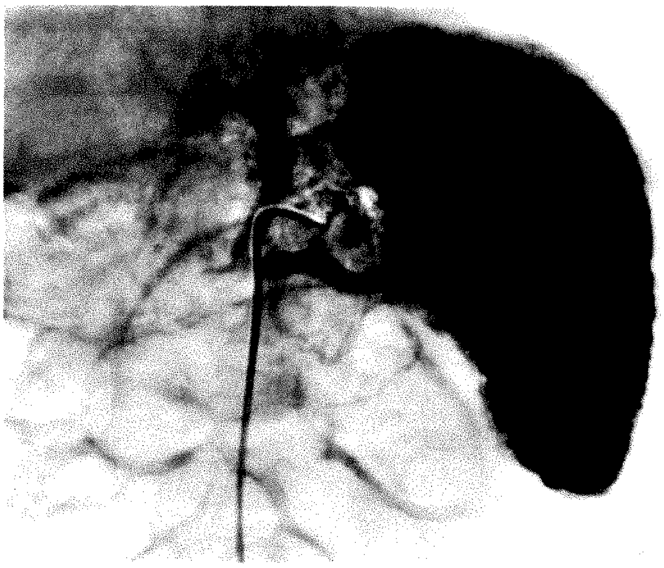

FIG. 6. Subtraction of the angiogram of Fig. 5. Enlarged spleen and stop in splenic vein are clearly visible. The catheter is still in the splenic artery.

When the aetiological factors persist (intimal lesion and stasis), the original platelet coagulum is transformed to a real thrombus by fibrinogenesis. Hoshal *et al.*[4] observed fibrinogenesis within 24 hours when using subclavian catheters, whether they be polyethylene, Teflon nylon or silicone rubber catheters. It was a conspicuous finding that polyethylene catheters pre-treated with graphite-benzalkonium chloride-heparin sodium (GBH) unmistakably gave less fibrinogenesis in this study. Whether this also applies to the much narrower splenic vein in neonates, however, remains a moot point.

Conclusion

Mechanical, chemical and infectious lesions of the intima, combined with a change in the blood flow rate, would seem to be the principal causes of the development of thrombosis following the use of an intravenous catheter.

Although there can be no doubt about the diagnostic, and particularly the therapeutic value of umbilical vein

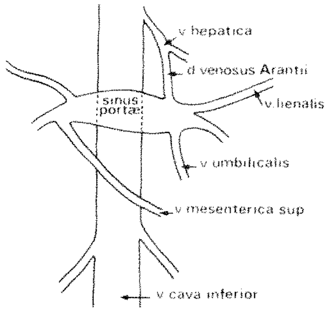

FIG. 7. Diagram of the neonatal portal system.

catheterization, the technique is not without its dangers. There are several possible complications. One such complication, hitherto unknown, is localized thrombosis of the splenic vein followed by splenomegaly and severe gastric and/or esophageal varices, as described in the above case reports. Since selective angiography of the mesenteric artery and splenic artery has become possible also in very young infants (Figs. 2–6), an exact preoperative diagnosis can be made. Treatment is technically simple: splenectomy. Perhaps it is advisable to confine surgery in infants to ligation of the splenic artery without splenectomy, with a view to the development of immunity.[2,5]

However, prevention is bettter than cure. The use of intravascular catheters, particularly in neonates, should be confined to cases which afford no alternative. If catheters have to be used, their calibre should be as small as possible; they should be very flexible in order to avoid fibrinogenesis (GBH-treated polyethylene catheters possible open new perspectives in this context). Their introduction requires strict asepsis, and the position of the catheter should always be fluoroscopically controlled. Infusion fluids which irritate the vascular wall must be avoided as much as possible. All intravascular catheters should be removed as soon as possible. It should always be borne in mind that, by introduction of an intravascular catheter, we place a time bomb inside the child.

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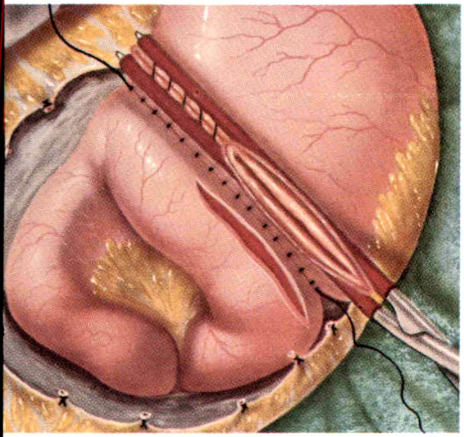
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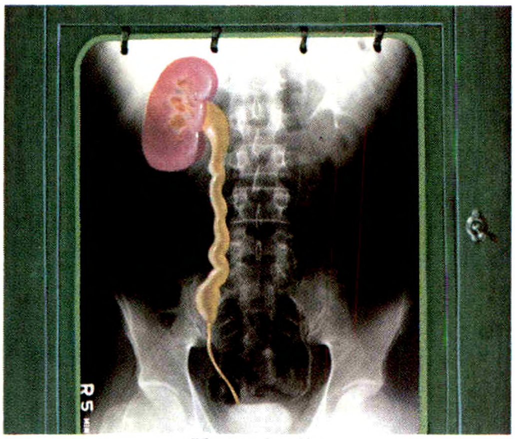

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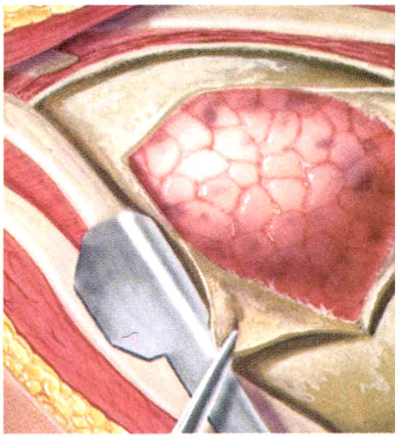
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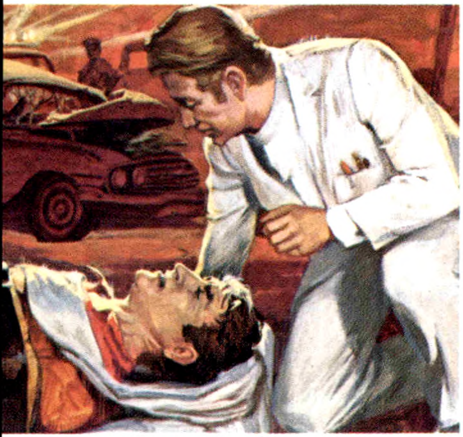
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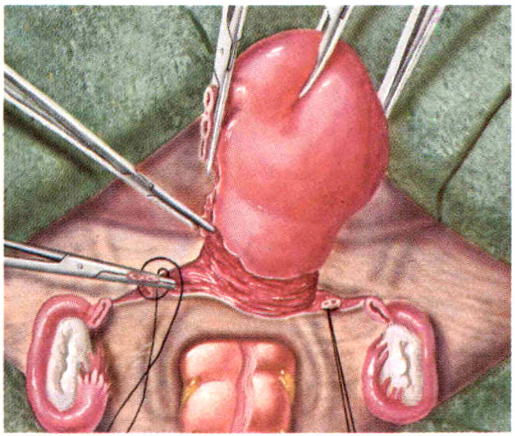
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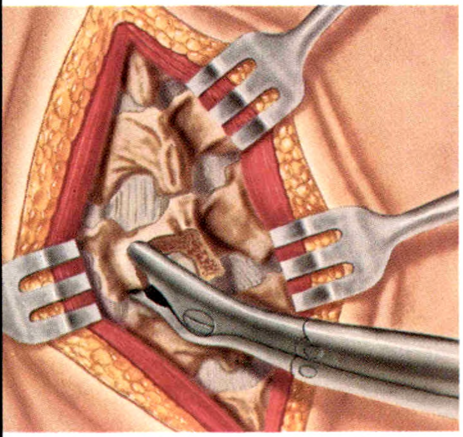
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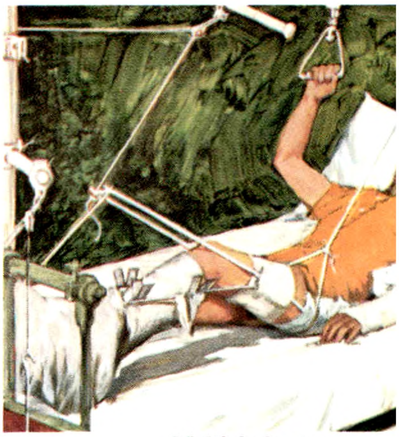
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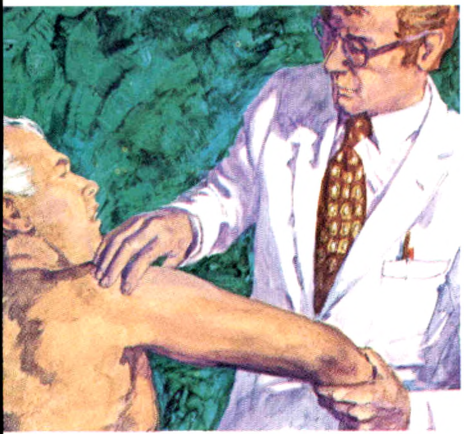
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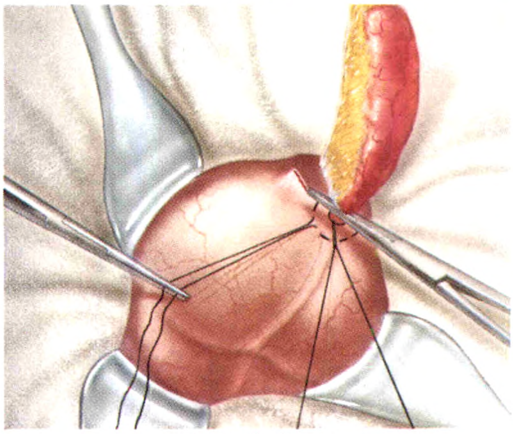
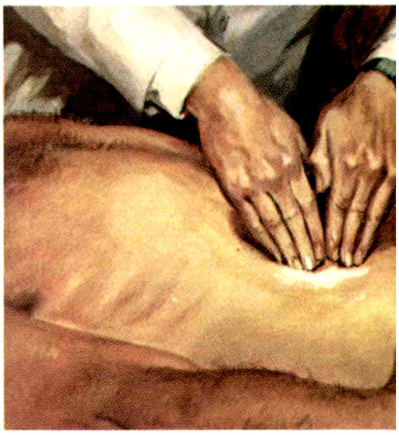

Appendectomy


Intestinal colic

Since clinical experience in children under 12 years of age is limited, the use of Talwin (brand of pentazocine, as lactate) in this age group is not recommended. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. See full instructions and warnings on last page.

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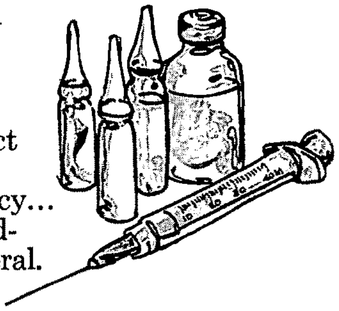
Talwin doesn't go to extremes.

Yet, Talwin relieves serious pain (moderate to severe pain) in the great majority of everyday hospital situations.



For most serious pain—Talwin has in fact been shown comparable to narcotics such as morphine and meperidine, in analgesic efficacy… with less likelihood of some of the extreme adverse effects produced by the opiates in general.

With Talwin there is a low incidence of respiratory depression, hypotension, urinary retention, and constipation.

In moderate to severe pain

Injectable Talwin®
brand of pentazocine (as lactate)

extremely effective for most patients

30 mg. 45 mg. 60 mg.

See important product information concerning warnings, adverse reactions, patient selection, prescribing and precautionary recommendations on last page of this advertisement.

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; *dermatologic:* soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Uni-Amp*T.M.*—Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.)* in boxes of 25.

Ampuls of 1½ ml. (45 mg.) in boxes of 10, 25, and 100.

Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

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McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg., **174**:58, 1971.

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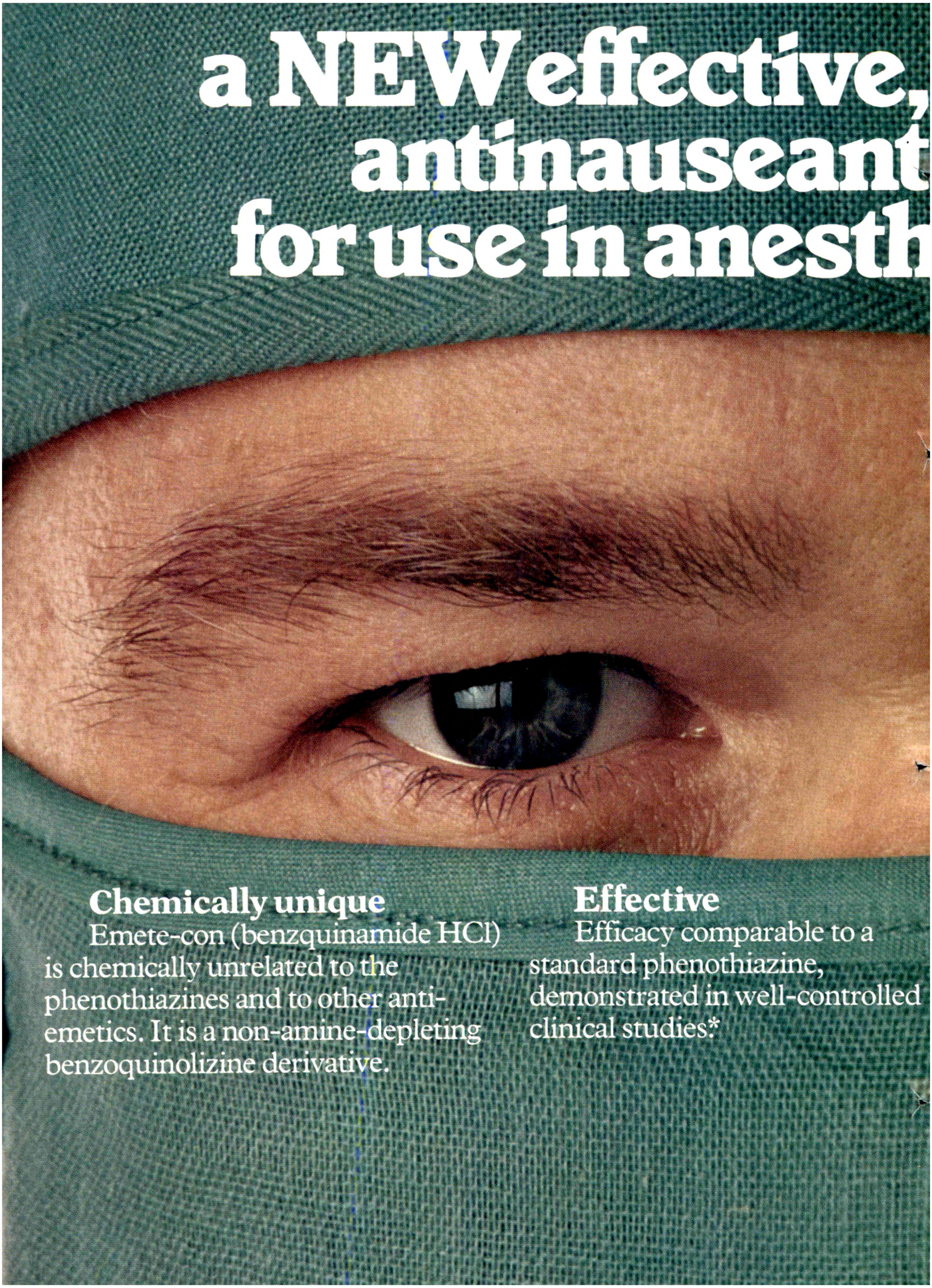

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Efficacy comparable to a standard phenothiazine, demonstrated in well-controlled clinical studies.*

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Drowsiness appears to be the most common reaction. Other more significant reactions have been reported; please refer to the package insert.

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Usual adult dose: IM-50 mg., IV-25 mg.

*Please see next page for a bibliography of clinical studies.

For prescribing information, including adverse reactions and contraindications, please see following page.

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For Intramuscular and Intravenous Use

Description. Benzquinamide is a non-amine-depleting benzoquinolizine derivative, chemically unrelated to the phenothiazines and to other antiemetics.

Chemically, Emete-con (benzquinamide-hydrochloride) is N, N-diethyl-1,3,4,6,7,11b-hexahydro-2-hydroxy-9, 10-dimethoxy-2H-benzo(a)quinolizine-3-carboxamide acetate hydrochloride. The empirical formula is $C_{22}H_{32}N_2O_5$. HCl and the molecular weight is 441.

Emete-con for injection contains: Benzquinamide HCl equivalent to benzquinamide 50 mg/vial and citric acid 1%. When reconstituted with 2.2 ml of sterile water for injection, each vial yields 2 ml of a solution containing benzquinamide, 25 mg/ml. When reconstituted, this product maintains its potency for 14 days at room temperature. DO NOT REFRIGERATE.

Actions. Benzquinamide HCl exhibited antiemetic, antihistaminic, mild anticholinergic and sedative action in animals. Studies conducted in dogs and human volunteers have demonstrated suppression of apomorphine-induced vomiting; however, relevance to clinical efficacy has not been established. The mechanism of action in humans is unknown. The onset of antiemetic activity in humans usually occurs within 15 minutes.

Benzquinamide metabolism has been studied in animals and in man. In both species, 5-10% of an administered dose is excreted unchanged in the urine. The remaining drug undergoes metabolic transformation in the liver by at least three pathways to a spectrum of metabolites which are excreted in the urine and in the bile, from which the more polar metabolites are not reabsorbed but are excreted in the feces. The half-life in plasma of Emete-con is about 40 minutes. More than 95% of an administered dose was excreted within 72 hours in animal studies using C14-labeled benzquinamide. In blood, benzquinamide is about 58% bound to plasma protein.

Indications. Emete-con is indicated for the prevention and treatment of nausea and vomiting associated with anesthesia and surgery.

Since the incidence of postoperative and postanesthetic vomiting has decreased with the adoption of modern techniques and agents, the prophylactic use of Emete-con should be restricted to those patients in whom emesis would endanger the results of surgery or result in harm to the patient.

Contraindications. Emete-con is contraindicated in individuals who have demonstrated hypersensitivity to the drug.

Warnings. *Use in Pregnancy:* No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children: As the data available at present are insufficient to establish proper dosage in children, the use of Emete-con in children is not recommended.

Intravenous use: Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route of administration should be restricted to patients without cardiovascular disease and receiving no pre-anesthetic and/or concomitant cardiovascular drugs.

Precautions. Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

Adverse Reactions. The following adverse reactions have been reported in subjects who have received benzquinamide. Because of the multiplicity of medications commonly used in the practice of anesthesia, unequivocal relationship to a specific drug administered usually cannot be established. However, drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected–*Autonomic Nervous System:* Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.

Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.

Gastrointestinal System: Anorexia, nausea.

Musculoskeletal System: Twitching, shaking/tremors, weakness.

Skin: Hives/rash.

Other Systems: Fatigue, chills, increased temperature.

Dosage and Administration. *Intramuscular:* 50 mg (0.5 mg/kg–1.0 mg/kg)

First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-con should be injected well within the mass of a larger muscle. The deltoid area should be used only if well developed. Injections should not be made into the lower and mid-thirds of the upper arm. Aspiration of the syringe should be carried out to avoid inadvertent intravascular injection.

Therapeutic blood levels and demonstrable antiemetic activity appear within fifteen minutes of intramuscular administration. When the objective of therapy is the prevention of nausea and vomiting, intramuscular administration is recommended at least fifteen minutes prior to emergence from anesthesia.

Intravenous: 25 mg (0.2 mg/kg–0.4 mg/kg as a single dose) administered slowly (1 ml per 0.5 to 1 minute). Subsequent doses should be given intramuscularly.

The intravenous route of administration should be restricted to patients without cardiovascular disease (See WARNINGS). If it is necessary to use Emete-con intravenously in elderly or debilitated patients, benzquinamide should be administered cautiously and the lower dose range is recommended.

This preparation must be initially reconstituted with 2.2 ml of sterile water. This procedure yields 2 ml of a solution equivalent to 25 mg benzquinamide/ml, which maintains its potency for 14 days at room temperature.
DO NOT REFRIGERATE.

Overdosage. *Manifestations:* On the basis of acute animal toxicology studies, gross Emete-con overdosage in humans might be expected to manifest itself as a combination of Central Nervous System stimulant and depressant effects. This speculation is derived from experimental studies in which intravenous doses of benzquinamide, at least 150 times the human therapeutic dose, were administered to dogs.

Treatment: There is no specific antidote for Emete-con overdosage. General supportive measures should be instituted, as indicated. Atropine may be helpful. Although there has been no direct experience with dialysis, it is not likely to be of value, since benzquinamide is extensively bound to plasma protein.

How Supplied. Emete-con for IM/IV use is available in a vial containing benzquinamide HCl equivalent to 50 mg of benzquinamide in packages of 10 vials.

Caution. Federal law prohibits dispensing without prescription.

Bibliography

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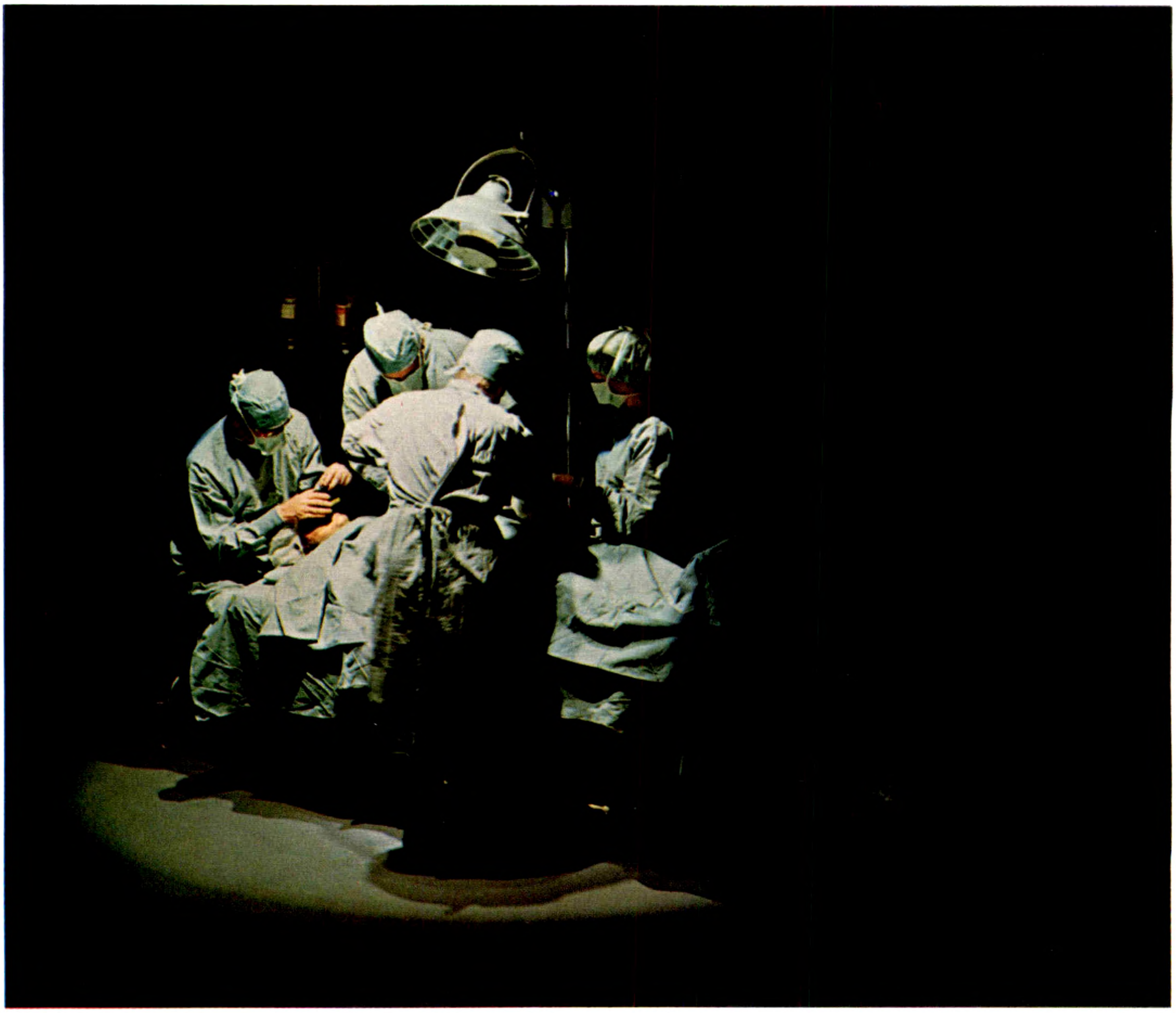

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Actions. *Human Pharmacology*—Following intramuscular administration of single 500 mg. and 1 Gm. doses to normal volunteers, average peak serum levels of 9.0 and 16.4 mcg./ml. respectively, were attained at 30 minutes, declining to 0.7 and 1.0 mcg./ml. respectively, at 4 hours and 0.2 and 0.3 mcg./ml. respectively, at 6 hours.

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Seventy percent of the administered dose was reccvered in the urine within 6 hours. Repetitive intravenous administration of 1 Gm. doses over 6-hour periods produced serum levels between 4.5 and 5.5 mcg./ml.

44 to 50% of Cefadyl is bound to human serum. The average serum half-life of Cefadyl in patients with normal renal function is approximately 36 minutes.

The major metabolite of cephapirin is desacetyl cephapirin which has been shown to contribute to antibacterial activity.

Controlled studies in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly. In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low.

Microbiology—*In vitro* tests demonstrate that the action of cephalosporins results from inhibition of cell-wall synthesis. Cefadyl is active against the following organisms *in vitro*:

Beta-hemolytic streptococci and other streptococci. (Many strains of enterococci, e.g., *S. faecalis*, are relatively resistant.)

Staphylococci, including coagulase-positive, coagulase-negative, penicillinase and non-penicillinase producing strains. *Diplococcus pneumoniae, Haemophilus influenzae, Proteus mirabilis, Escherichia coli*, Klebsiella species.

Most strains of enterobacter and indole-positive Proteus *(P. vulgaris, P. morganii, P. rettgeri)* are resistant to Cefadyl. Methicillin-resistant staphylococci, Serratia, Pseudomonas, Mima and Herellea species are almost uniformly resistant to Cefadyl.

Disc Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to cephalosporin class antibiotics. Interpretations correlate diameters of the disc test with MIC values for Cefadyl. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Indications. Cefadyl is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Group A beta-hemolytic streptococci: Skin and soft tissue infections. Respiratory infections.

(Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefadyl is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cefadyl in the subsequent prevention of rheumatic fever are not available at present.)

Staphylococcus aureus (penicillinase producing and non-penicillinase producing): Skin and soft tissue infections. Urinary tract infections.

Diplococcus pneumoniae: Respiratory tract infections.

Haemophilus influenzae: Respiratory tract infections.

Escherichia coli: Urinary tract infections, skin and soft tissue infections and bacteremia.

Klebsiella species: Urinary tract and respiratory tract infections.

Proteus mirabilis: Urinary tract infections.

Note: Appropriate bacteriological studies should be performed to identify the causative organisms and determine its susceptibility. Therapy may be started while awaiting results of these studies.

Contraindications. Cefadyl (sterile cephapirin sodium) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings. IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exceptions should be made with regard to Cefadyl.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions. The renal status of the patients should be determined prior to and during Cefadyl (sterile cephapirin sodium) therapy, since in patients with impaired renal function, a reduced dose may be appropriate (see *Dosage, Adults*). When Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported.

Prolonged use of Cefadyl may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Adverse Reactions. *Hypersensitivity*—Cephalosporins were reported to produce the following reactions: maculopapular rash, urticaria, reactions resembling serum-sickness, and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—During large scale clinical trials, rare instances of neutropenia, leukopenia, anemia were reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs test during therapy with other cephalosporins.

Liver—Elevations in SGPT or SGOT, alkaline phosphatase, and bilirubin have been reported.

Kidney—Rises in BUN have been observed; their frequency increases in patients over 50 years old.

Dosage. *Adults*—The usual dose is 500 mg. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. The lower dose of 500 mg. is adequate for certain infections, such as skin and soft tissue and most urinary tract infections. However, the higher dose is recommended for more serious infections.

Very serious or life-threatening infections may require doses up to 12 Grams daily. The intravenous route is preferable when high doses are indicated.

Depending upon the causative organism and the severity of infection, patients with reduced renal function (moderately severe oliguria or serum creatinine above 5.0 mg./100 ml.) may be treated adequately with a lower dose, 7.5 to 15 mg./Kg. of cephapirin every 12 hours. Patients with severely reduced renal function and who are to be dialyzed should receive the same dose just prior to dialysis and every 12 hours thereafter.

Children—The dosage is in accordance with age, weight and severity of infection. The recommended total daily dose is 40 to 80 mg./Kg. (20 to 40 mg./lb.) administered in four equally divided doses.

The drug has not been extensively studied in infants; therefore, in the treatment of children under the age of three months the relative benefit/risk should be considered.

Therapy in beta-hemolytic streptococcal infections should continue for at least 10 days.

Where indicated, surgical procedures should be performed in conjunction with antibiotic therapy.

Administration. Cefadyl may be administered by the intramuscular or the intravenous routes.

Intramuscular Injection—The 1 Gm. vial should be reconstituted with 2 ml. of Sterile Water for Injection, U.S.P. Each 1.2 ml. contains 500 mg. of cephapirin. All injections should be deep in the muscle mass.

Intravenous Injection—The intravenous route may be preferable for patients with bacteremia, septicemia, or other severe or life-threatening infections who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending. If patient has impaired renal function, a reduced dose may be indicated (see *Dosage, Adults*). In conditions such as septicemia, 6 to 8 Gm. per day may be given intravenously for several days at the beginning of therapy; then, depending on the clinical response and laboratory findings, the dosage may gradually be reduced.

When the infection has been refractory to previous forms of treatment and multiple sites have been involved, daily doses up to 12 Gm. have been used.

Intermittent Intravenous Injection—The contents of the 1 Gm. vial should be diluted with 10 ml. or more of diluent and administered slowly over a 3 to 5 minute period or may be given with intravenous infusions.

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Continuous Intravenous Infusion—After reconstitution, Cefadyl may be added to the solutions listed below under *Stability*. The choice of solution and volume should be dictated by the fluid and electrolyte management of the patient.

Stability. *Storage Stability*—After reconstitution, Cefadyl is stable for 12 hours at room temperature and 10 days under refrigeration when reconstituted with Sterile Water for Injection, U.S.P. The pH of the resultant solution ranges from 6.5 to 8.5. During these storage conditions, no precipitation occurs. A change in solution color during this storage time does not affect the potency.

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*Bauer, A.W., Kirby, W.M.M., Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol., 45:493, 1966. Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972.

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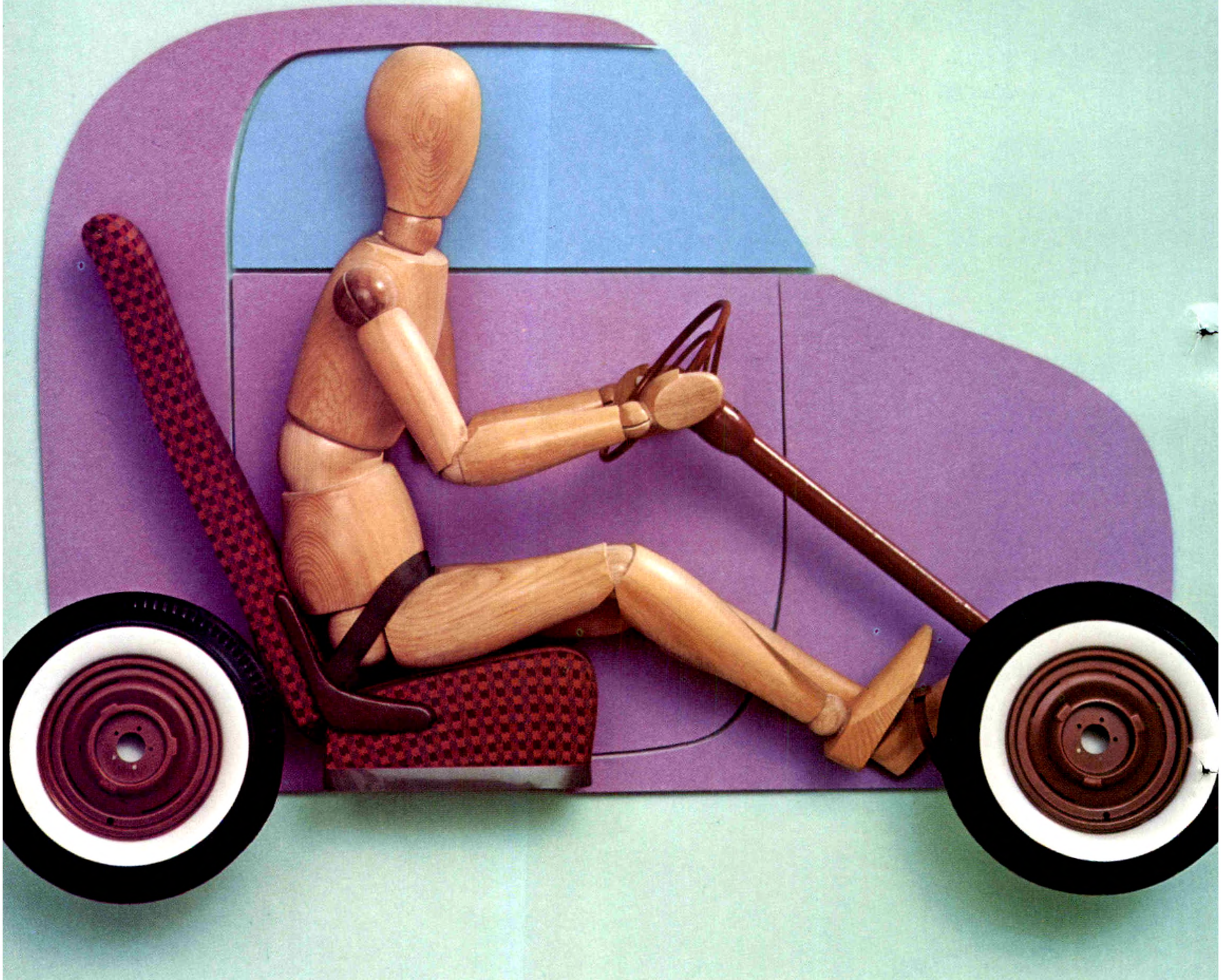

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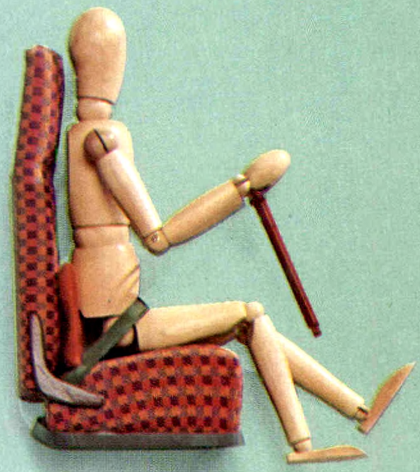

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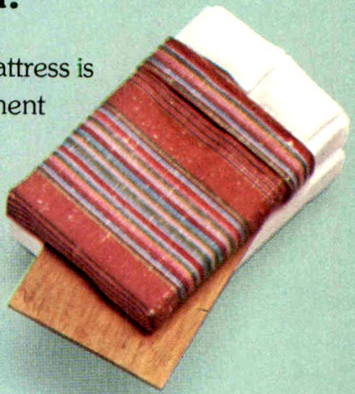

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Neoplasms of the Small Bowel

HOWARD SILBERMAN, M. D., ROBERT W. CRICHLOW, M.D.,*
HOWARD S. CAPLAN, M.D.

Small bowel tumors are unusual lesions exhibiting nonspecific clinical features often diagnosed at an advanced stage. In the cases studied at the Hospital of the University of Pennsylvania nearly all the 32 patients with malignancies were symptomatic whereas in the 34 patients with benign lesions the condition was discovered as an incidental finding in about half of the patients. Weight loss, palpable mass or anemia usually indicated malignancy. Small bowel radiography was the most useful diagnostic aid in the present series. While the etiology of these lesions is unknown, villous adenomas probably bear a relationship to carcinoma. The association between chronic regional enteritis and small bowel tumors is unestablished but suggestive. An analysis of reported series reveals a disproportionate incidence of additional primary tumors in patients with small bowel neoplasms. Surgical extirpation is indicated for curative treatment. In the present series, resection in hope of cure was carried out in 25 of 32 malignant tumors resulting in eight five-year survivals. One of these latter lived nine years with disseminated malignant carcinoid reflecting the occasional indolent course of this tumor.

THOUGH REPRESENTING 75% of the length and over 90% of the mucosal surface area of the alimentary tract, the small intestine is the site of only 3–6% of gastrointestinal neoplasms[1] and approximately 1% of malignant tumors.[8] Only 650 malignant small bowel tumors were recorded in the literature between 1920 and 1965;[18] merely 60 malignancies were found among nearly one million patients admitted to Charity Hospital in New Orleans.[7]

Prompt recognition and expeditious treatment of these lesions are unusual not only as a consequence of their infrequency, but also because of the often vague and non-specific manifestations they produce.

From the Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Improved management of these rare neoplasms depends upon appreciation of their clinical and pathologic features knowledge of which necessarily derives from the combined experience of many institutions.

The present study analyzes the experience with primary small bowel tumors at the Hospital of the University of Pennsylvania.

Clinical Material

Thirty-two malignant and 34 benign neoplasms of the small intestine were diagnosed at the Hospital of the University of Pennsylvania between 1950 and 1970. All lesions included in this analysis were identified histologically following operation or autopsy. Patients ranged 35–79 years of age. Average age at diagnosis was 59.5 years. Patients harboring malignant lesions average 56.8 years compared to 62.2 years for patients with benign lesions.

Malignant lesions were divided equally between males and females, but 23 of the 34 benign lesions were in men.

Thirty of the 32 malignant lesions produced clinical manifestations (Table 1). Weight loss was the most common finding in these patients; it was recorded in 17 instances. Fifteen patients complained of pain evidently related to bowel obstruction or local tumor invasion. Nausea or vomiting occurred in 11 patients, and bleeding, manifest as hematochesis or melena, was reported in eight.

Anemia (hemoglobin less than 10.5 gm%) was the most common clinical sign associated with small bowel malignancy and was encountered in 13 of these patients. Physical examination revealed an abdominal mass in seven and jaundice in two. Obstruction, either partial or complete, was documented in six cases of which two

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Submitted for publication November 5, 1973.

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Reprint requests: Howard Silberman, M.D., Department of Surgery, USAF Medical Center, Scott, Scott AFB, Illinois 62225.

TABLE 1. *Clinical Manifestations of Small Bowel Tumors*

	Malignant Tumors (32)	Benign Tumors (34)
Symptomatic	30 (94%)	18 (53%)
Weight loss	17 (53%)	6 (17%)
Pain	15 (47%)	14 (40%)
Anemia	13 (41%)	5 (15%)
Nausea or vomiting	11 (34%)	8 (24%)
GI bleeding	8 (25%)	11 (32%)
Mass	7 (22%)	1 (3%)
Obstruction	6 (19%)	7 (21%)
Diarrhea	5 (16%)	3 (9%)
Constipation	4 (13%)	2 (6%)
Jaundice	2 (6%)	0 (0%)
Asymptomatic	2 (6%)	16 (47%)
Autopsy finding	2 (6%)	12 (35%)
Clinical or operative finding	0 (0%)	4 (12%)

were due to intussusception. Two patients were asymptomatic; their lesions were incidental findings at operation for other cause.

Of eight patients with malignant carcinoid, six presented with weight loss, and diarrhea and pain were each reported by five patients. Flushing associated with elevated levels of urinary 5-hydroxy-indole acetic acid occurred in two patients.

In contrast to malignant lesions, 16 of the benign tumors including nine carcinoids were incidental findings at autopsy, operation, or during clinical evaluation of unrelated symptoms. Among symptomatic patients, abdominal pain was the most prominent feature, occurring in 14. Rectal bleeding occurred in ten; one patient presented with hematemesis. Nausea, vomiting, weight loss, diarrhea, and constipation occurred among these patients but infrequently (Table 1).

Signs of obstruction were present in seven patients with benign lesions. Intussusception was responsible for the obstructive picture in two of these instances and caused the mass palpated in one patient. Five individuals were anemic.

Of 48 symptomatic patients, 27 reported symptoms of at least six months' duration. Eighteen of the 27 had malignant lesions. Among symptomatic patients, nine malignancies and six benign neoplasms were symptomatic over one year prior to diagnosis (Table 2).

The preoperative diagnosis of small bowel neoplasm was made in 28 cases in this series. Accurate preoperative diagnosis was made in 17 (53%) of the patients harboring malignancies. In 15 of these 17 cases, barium studies of the upper gastrointestinal tract including the small bowel ("long GI series") revealed the lesion. Two additional malignant lesions were diagnosed by identifying the features of the carcinoid syndrome. Nine symptomatic and two asymptomatic patients with benign lesions were diagnosed preoperatively by means of long GI series. Two other patients had abnormalities described in long GI series (mass, partial small bowel obstruction), but the diagnosis of small bowel tumor was not entertained. Nineteen additional patients had films interpreted as showing a normal small bowel pattern. Thus, 26 of 41 long GI x-ray examinations revealed the lesion. Barium enema examination revealed an ileal lesion by reflux of barium into the ileum in two cases.

TABLE 2. *Duration of Symptoms*

	Malignant Tumors (30)	Benign Tumors (18)
0–5 days	5	5
5 days–2 months	3	1
2 mos.–6 mos.	4	3
6 mos.–1 year	9	3
More than 1 year	9	6

The histologic and anatomic distribution of the lesions encountered in this series is presented in Table 3. The 32 malignancies were distributed generally throughout the small bowel. However, over half of the 19 adenocarcinomas were duodenal. Three-quarters of the malignant carcinoids were located in the ileum. A wide variety of benign lesions was identified, but leiomyomas and benign carcinoids accounted for one-third of the lesions. Nine of the ten benign carcinoids were found in the ileum.

Thirteen of the patients in this series had 14 other primary tumors outside of the small bowel. The small bowel lesion in seven of these patients was carcinoid (Table 4).

Treatment and Prognosis

Twenty-one patients with benign small bowel lesions had an operative procedure. The procedures performed included 13 wedge resections, four polypectomies, one

TABLE 3. *Histologic and Anatomic Distribution of Small Bowel Tumors*

	Total	Duodenum	Jejunum	Ileum
Adenocarcinoma	19	10	5	4
Malignant carcinoid	8	0	2	6
Leiomyosarcoma	4	1	2	1
Lymphosarcoma	1	0	0	1
Malignant tumors	32	11	9	12
Leiomyoma	12	4	7	1
Benign carcinoid	10	1	0	9
Hemartoma	3	2	1	0
Inflammatory polyp	2	0	0	2
Lymphangioma	2	1	1	0
Lipoma	2	0	1	1
Brunners gland polyp	1	1	0	0
Endometriosis	1	0	0	1
Leiomyoblastoma	1	0	1	0
Benign tumors	34	9	11	14
All tumors	66	20	20	26

gastrectomy for carcinoid of the first part of the duodenum, and one right hemicolectomy for an ileal carcinoid. A duodenal leiomyoma and a duodenal lymphangioma were incidental findings in gastrectomy specimens in two patients operated upon for peptic ulcer disease.

The treatment and survival data for patients with malignant lesions are tabulated in Table 5. Of 11 patients with duodenal malignancies, nine underwent treatment intended to cure. Three adenocarcinomas were extirpated by wedge resection and three by polypectomy. Two patients were treated by radical pancreaticoduodenectomy (Whipple operation). No five-year cures were achieved. An additional patient had a palliative bypass and another had no operative procedure. A leiomyosarcoma of the duodenum was managed by pancreaticoduodenectomy. This patient died four years postoperatively free of disease.

Seven jejunal malignancies, including one malignant carcinoid, four adenocarcinomas and two leiomyosarcomas were treated by wide wedge resection for cure. Two patients with adenocarcinoma and one with leiomyosarcoma survived five years. Two patients underwent palliative resection. One patient with malignant carcinoid with metastases survived nine years following a palliative resection, the latter six years with the carcinoid syndrome.

Curative resection, including two right hemicolectomies, was performed in nine patients with ileal malignancies. Five-year cure was achieved in two of four malignant carcinoids, one of three adenocarcinomas and in the sole instance of lymphosarcoma. The latter was treated by right hemicolectomy and postoperative irradiation. Hemicolectomy for an ileal adenocarcinoma failed to eradicate the disease.

TABLE 4. *Other Neoplasms in Patients with Small Bowel Tumors*

Small Bowel Tumor	Other Primary Tumor
Benign Carcinoid (ileum)	Carcinoma of Esophagus
Benign Carcinoid (ileum)	Carcinoma of Cervix
Benign Carcinoid (ileum)	Leiomyoma of Stomach
Benign Carcinoid (ileum)	Carcinoma of Gall bladder
Malignant Carcinoid (jejunum)	Carcinoma of Rectum
Malignant Carcinoid (ileum)	Papillary Carcinoma of Bladder
Carcinoma (duodenum)	Carcinoma of Cervix
Carcinoma (duodenum)	Carcinoma of Colon
Lipoma (jejunum)	Carcinoma of Lung
Leiomyoma (duodenum)	Carcinoma of Colon
Leiomyoma (duodenum)	Carcinoma of Prostate Retroperitoneal liposarcoma
Leiomyosarcoma (jejunum)	Carcinoma of Prostate

Thus, 25 patients with malignancy were subjected to operation intended for cure: 17 wedge resections, three radical pancreaticoduodenectomies, three polypectomies, and two hemicolectomies. Seven five-year cures were achieved. An additional patient died at four years free of disease, and another died nine years following palliative resection.

Discussion

Reported series indicate that small bowel tumors are rare lesions which generally occur later in life, the median age of diagnosis being in the sixth decade. There is a slight predominance of occurrence in males.[7,14,15,19]

TABLE 5. *Malignant Tumors: Treatment & Survival*

	Total	Operation			5 Year Survival	Lost to Followup
		Curative	Palliative	None		
Adenocarcinoma						
Duodenum	10	8	1	1	0	2
Jejunum	5	4	1	0	2	0
Ileum	4	3	1	0	1	0
	19	15	3	1	3	2
Malignant Carcinoid						
Jejunum	2	1	1	0	1*	0
Ileum	6	4	2	0	2	0
	8	5	3	0	3	0
Leiomyosarcoma						
Duodenum	1	1†	0	0	0	0
Jejunum	2	2	0	0	1	0
Ileum	1	1	0	0	0	0
	4	4	0	0	1	0
Lymphosarcoma						
Ileum	1	1‡	0	0	1	0
All Malignancies	32	25	6	1	8	2

* Patient had palliative resection, lived 9 years with metastases.
† Patient died at four years free of disease.
‡ Patient received radiotherapy postoperatively.

Clinical Features

A wide variety of protean manifestations occur with these lesions. Abdominal pain, nausea, vomiting, weight loss, palpable mass, and anemia are the commonest and most characteristic symptoms.[5-7,14,15,19] Dorman[7] identified cramping abdominal pain, weight loss, and a palpable mass as a "diagnostic triad of paramount importance." Peripapillary lesions frequently produce jaundice. Weight loss and a palpable mass, when present, tend to distinguish malignant from benign lesions;[5] however, a mass was recorded in only five of 77 patients with malignancies at the Lahey Clinic.[1]

Diagnosis

Although over 90% of malignant tumors produce symptoms[1,8,19] diagnosis is frequently delayed for long periods. A correct preoperative diagnosis was made in 53% of symptomatic patients reported by Strauch[24] and in only 21% reported by Ostermiller.[14]

Preoperative diagnosis was made radiographically in about 50% of patients with malignancy in the present series. Small bowel radiography revealed abnormalities in 14 of 19 studies in patients subsequently shown to have malignant lesions at Johns Hopkins Hospital.[8] In addition to the characteristic x-ray findings in obstruction and intussusception, Good has identified several radiographic patterns seen in barium contrast studies of the small bowel.[9] Local filling defects in the barium column may be 1) intraluminal, 2) mucosal or ulcerating, or 3) intramural. Intraluminal filling defects are most commonly caused by adenomatous polyps, but other lesions such as leiomyomas may become pedunculated and produce this picture. Mucosal or ulcerating defects are often caused by adenocarcinoma or lymphomas. Lesions arising intramurally such as lymphomas or sarcomas may encroach upon the lumen but the mucosa remains intact. In contrast, such lesions growing outward, rather than compromising the lumen, may produce a clinically palpable mass which correlates radiographically with displacement of adjacent small bowel loops.[1,6,9,18]

Pathology

Sarcomas, lymphomas, and carcinoids increase in incidence progressively from the duodenum to ileum. In contrast, adenocarcinomas are nearly evenly distributed between the duodenum, jejunum, and ileum with perhaps slight predominance in the duodenum.[2,18] Twenty per cent of duodenal adenocarcinomas are peripapillary; the remainder are divided evenly between supra- and infra-papillary locations.[18]

Adenocarcinoma is the most common variety of malignant tumor affecting the small bowel, representing nearly one-half of such lesions.[18] Excluding carcinoids, lymphomas follow adenocarcinoma in frequency of occurrence.[12] Lymphosarcoma, reticulum cell sarcoma, and Hodgkin's disease occur in decreasing order of frequency. Of 48 lesions studied at the Mount Sinai School of Medicine,[13] there were 31 lymphosarcomas, ten reticulum cell sarcomas, and seven cases of Hodgkin's disease. The age, sex distribution, and clinical manifestations of these lesions were similar to the general features of small bowel lesions described above.

Leiomyosarcomas are characterized by their intramural origin, the large size they attain, and their vascular nature producing a high incidence of bleeding.[6,10]

Etiology

In general, the etiology of small bowel neoplasms is unknown. However, the multiple polypoid hamartomas of the Peutz-Jeghers syndrome are inherited as a Mendelian dominant trait.[6]

Small bowel villous adenomas appear to bear the same relationship to carcinoma as colonic lesions.[11,22] In a review of the literature from Cleveland Clinic, 27 cases of small intestinal villous adenomas were collected.[11] Of 20 duodenal lesions, five contained invasive adenocarcinoma, two focal carcinoma, and one *in situ* carcinoma. Among seven jejunal villous adenomas two contained invasive carcinoma and one "superficial" carcinoma.

Whereas a clear association exists between long standing ulcerative colitis and subsequent colon carcinoma, the relation between chronic inflammatory disease and malignancy of the small bowel is unestablished. However, recent reports suggest such an association may exist.[3,4,17,21,25] Twenty-five cases of small bowel adenocarcinoma complicating chronic regional enteritis have been reported. Nine of these tumors have occurred in segments of small bowel previously bypassed because of Crohn's disease. Tyers[25] and Steiger[21] point out that adenocarcinomas arising in patients with regional enteritis differ from the usual lesions in that they occur at an earlier age (average 42.9 years), their distribution parallels that of the inflammatory disease (69% in ileum), and the prognosis is grave (no five-year survivals).

A high incidence of additional primary tumors occurs in patients with small bowel neoplasms. Reyes and Talley[16] reported an incidence of second primary neoplasms outside the small intestine of 17.7% compared to 0.33% noted in the average population. In that series, 11 of 62 patients had 13 second primary tumors including three basal cell carcinomas and three rectal adenocarcinomas. Second primary malignancies occurred in 10 of 60 patients, in 12 of 61 patients, and in six of 47 patients in series reported by Dorman,[7] Ostermiller[14] and Strauch[24] respectively.

Treatment

Curative treatment for malignant lesions entails wide resection with the adjacent mesentery. In McPeak's view[10] adequate management requires pancreaticoduodenectomy for duodenal lesions and right hemicolectomy for distal ileal lesions. Opinions regarding the adjuvant role of radiotherapy in lymphomas vary. Sternlieb[23] recommends it; Weaver[26] questions the value of radiotherapy in patients in whom lymph nodes are negative and the tumor has been removed.

Patients with metastatic carcinoid appear to benefit by the reduction in tumor burden achieved by palliative resection of primary and metastatic tumor. Brookes[2] reports a 33% five-year survival rate after palliative surgery.

Prognosis

The prognosis for adenocarcinoma is grim. Five-year survival figures range from 16.4 to 32% in reported series.[2,7,15,19] Corresponding figures for lymphoma range between 31–40%.[13,15] A 48% five-year survival rate following resection of leiomyosarcoma was reported by Pagtalunan.[15]

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Fluid Replacement Monitoring:

Effect of Dextran Overload, Norepinephrine Drip, and Positive Pressure Ventilation on Systemic Arterial, Right Atrial Pulmonary Wedge, and Left Atrial Pressures in Dogs

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The effects of dextran overload, norepinephrine drip and positive pressure ventilation upon right atrial, pulmonary wedge, left atrial and systemic arterial pressures were studied in 15 dogs. Rapid intravenous infusion of Dextran 70 invariably produced a marked and statistically significant ($p < .001$) rise in right atrial, pulmonary wedge and left atrial pressures. The rise in left atrial pressure invariably exceeded the rise in right atrial pressure, and the difference in maximum pressures averaged 10.8 mm Hg ($p < .001$). Thus acute fluid overload and pulmonary edema can be produced by rapid infusion of colloid solution in the absence of a marked rise in right atrial pressure, a point of considerable clinical importance. The rapid infusion of dextran produced a rise in systemic arterial blood pressure in all dogs so studied, though this rise was mild in some animals. This finding may explain in part the hypertension exhibited by patients in the recovery room who may have been overtransfused. A norepinephrine drip usually produced an increase in right atrial, wedge, left atrial and systemic arterial blood pressure ($p < .01$). When there was a significant rise in right atrial pressure and left atrial pressure, the maximum increase in left atrial pressure was always greater than the maximum increase in right atrial pressure ($p < .005$). This finding again emphasizes the fact that blood transfusion requirements cannot always be accurately assessed on the basis of right and left atrial pressure measurements when a vasopressor agent is being administered. Positive pressure ventilation increased both right and left atrial pressures, as expected. It was again confirmed that pulmonary wedge pressure, as measured with the Swan-Ganz catheter, is approximately equal to left atrial pressure over a wide range of induced variations. The Swan-Ganz catheter, introduced at the bedside in the intensive care unit when necessary, can provide highly useful information regarding left atrial pressure and left ventricular end-diastolic pressure.

APPROPRIATE FLUID REPLACEMENT THERAPY represents a major requirement for successful surgical practice. Forty years ago a liter of blood was viewed as a substantial transfusion, and so-called irreversible shock was commonplace. Similarly, the hugh third space fluid losses which occur in burns, peritonitis and blunt trauma were only beginning to be recognized. However, experience with the management of casualties in World War II and more recent conflicts established the fact that many instances of what would previously have been designated irreversible shock were in fact reversible, if accurate diagnosis was followed by appropriate blood volume replacement, aid to respiration, treatment of sepsis, and support of the failing heart. In fact, cases of truly irreversible shock early in the course of traumatic injury have become uncommon. However, the need for the rapid infusion of large volumes of colloid or electrolyte solution has rendered ever more important the measurements available to serve as dependable and safe guides to fluid replacement.

The purpose of this study was to compare the effects of dextran overload, norepinephrine drip, and positive

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pressure ventilation on systemic arterial, pulmonary wedge, right atrial, and left atrial mean pressures. The following questions were posed: 1) To what extent would right atrial, pulmonary wedge and left atrial pressures rise during dextran overload, norepinephrine drip, or positive pressure ventilation? 2) What was the probable mechanism for the development of the pulmonary edema induced in patients by rapid colloid infusion, when right atrial pressure remained within normal limits? 3) Could the systemic arterial hypertension occasionally observed in the Recovery Room be due to excessive blood transfusion, in addition perhaps to vasoconstriction caused by an increased circulating level of endogenous catechol amines? 4) Were the pulmonary wedge pressures in fluid overload, as measured with the Swan-Ganz catheter, approximately equal to the left atrial pressures as measured directly?

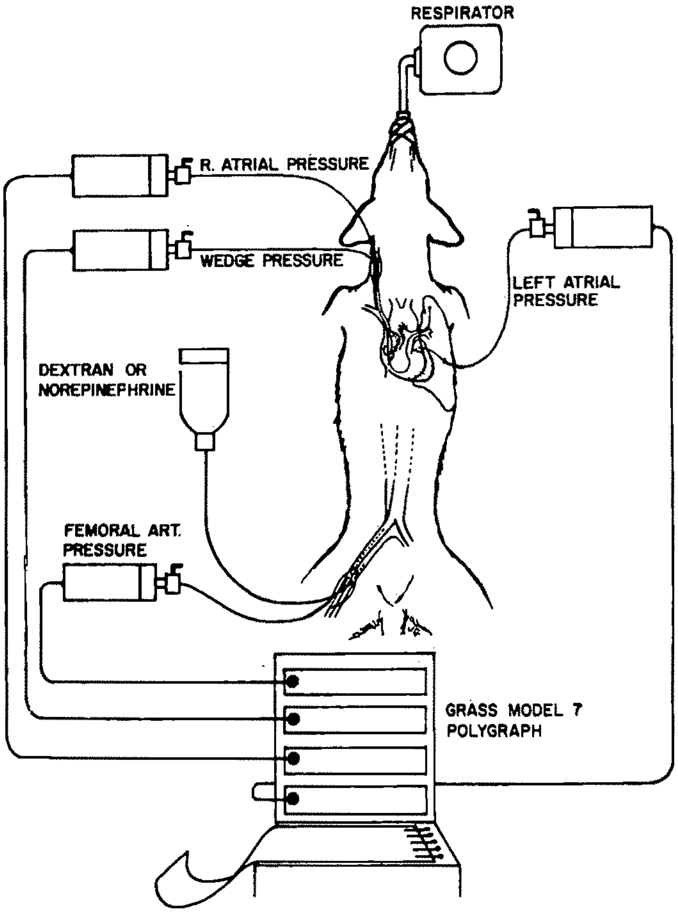

Fig. 1. The experimental model.

Methods

Fifteen dogs averaging 19 kg each served as their own controls for the three experimental conditions: norepinephrine administration, positive pressure ventilation and dextran overload infusion. Each dog received 8–12 cc of 5% pentobarbital before a catheter was inserted into the right femoral artery to record systemic pressure and ECG electrodes were attached. Next, No. 4 Swan-Ganz catheters (4) were placed in the pulmonary wedge position and the right atrium via the right external jugular vein. The position of each catheter was determined by observing pressure changes on the Minneapolis Honeywell visi-recorder, as the catheter was advanced. In addition, the position of this catheter was checked by palpation at left thoracotomy in a number of animals.

Next, the dog was supported by a cuffed endotracheal tube and ventilator (20 cm H_2O) while the chest was opened and a No. 5 Swan-Ganz catheter was inserted into the left atrium and its balloon inflated. A 30-minute rest period followed the closing of the chest and removal from the respirator. A chest drainage tube was placed under water seal. All four catheters were connected to transducers (Fig. 1) and "mean" pressures were recorded, obtained by "damping down" the recording needle.

In a counterbalanced order to permit statistical analysis, and separated by a ten minute rest period, the norepinephrine (Levophed) and positive pressure treatments followed. In the former condition Levophed (8 mg/500 ml of lactated Ringer's solution) was introduced into a femoral vein at 80–100 drops/min, until systemic pressure rose. At this point, the rate was reduced to 20–24 drops/min and right atrial, pulmonary wedge, left atrial and systemic pressures were recorded for five minutes. The positive pressure ventilation (20 cm H_2O) also lasted five minutes. Pilot studies indicated that, for various mechanical and perhaps physiological reasons, a given initial rate of norepinephrine infusion did not give a definite circulatory response in every dog. Therefore, in subsequent experiments the drip was simply continued at a brisk rate until a definite response was obtained. This procedure was considered acceptable in that the objective was to compare pressure levels during a norepinephrine response, not to determine the precise norepinephrine dosage which produced a definite response in the given animal.

Following a second ten minute rest period, large molecular weight dextran (Dextran 70) was infused (5% body weight) at approximately 100 ml/min. Again, all pressures were recorded and final readings were taken one hour after completion of the infusion. While for statistical purposes it might have been desirable to counterbalance the dextran and the norepinephrine infusions, this was not possible because of the prolonged retention of dextran, once given, in the bloodstream and other body fluids.

The effects of positive pressure ventilation levels of 20 cm, 30 cm, and 40 cms of water were examined in three additional dogs. The catheters were withdrawn at the end of the experiment and animal survival was achieved in most instances.

The pressure changes were analyzed statistically using t-tests.

Results

Fifteen dogs were studied. The results of dextran overload and norepinephrine drip are presented in Fig. 2 and the several levels of positive pressure ventilation in Fig. 3.

Norepinephrine Infusion by Drip

Since vasopressor drugs are often used while further blood and fluid therapy are under consideration, it appeared desirable to re-examine the hemodynamic effect of this drug in association with the other parameters of this investigation.

The norepinephrine drip usually produced an increase in systemic, right atrial, wedge and left atrial pressure ($p < .01$). When there was a significant difference in right atrial pressure and left atrial pressure, the maximum increase in left atrial pressures (Fig. 2) was always greater than the maximum increase in right atrial pressure (13.5 mm Hg average difference). This difference was statistically significant ($p < .005$). As mentioned previously, the pulmonary "wedge" pressure was often higher than the left atrial pressure at the peak rise produced by the norepinephrine drip. Again, it is suggested that this level may in part have reflected proximal pulmonary artery pressure.

In any event, the need for blood replacement, as reflected in right atrial and left atrial pressures, cannot be accurately assessed when the patient is receiving norepinephrine. This probably holds true for other vasopressor drugs as well. Norepinephrine was selected for our studies because of the vigor of the cardiovascular response which it produces.

Dextran Overload

The infusion of 100 ml of dextran per minute for approximately 10 minutes, depending upon the weight of the given dog, invariably produced a marked and statistically significant ($p < .001$) rise in right atrial, wedge and left atrial pressures (Fig. 2). The wedge pressure was frequently but not invariably higher than the left atrial pressure, a difference which suggested that when the pulmonary artery was distended by abnormal pressure the balloon on the Swan-Ganz catheter did not totally exclude communication with the pulmonary artery pressure proximally. This possibility was further supported by the fact that the pulmonary wedge pressure was also greater than left atrial pressure when norepinephrine was administered. But in general, pulmonary wedge pressure

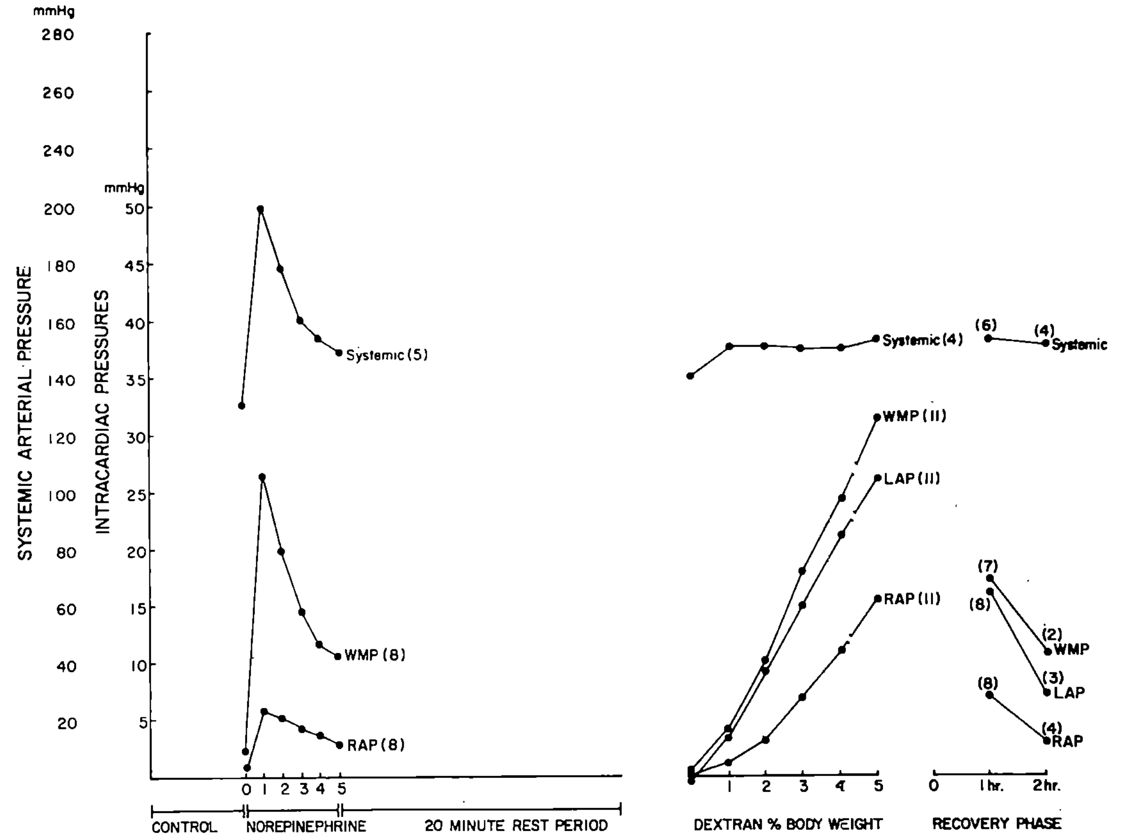

FIG. 2. Effect of norepinephrine and dextran overload on intracardiac and systemic pressures. Norepinephrine infusion increased the right atrial pressure (RAP) wedge mean pressure (WMP) and systemic arterial pressure. The numerals in parentheses indicate the number of animals whose data were employed to construct a given curve. Dextran 70 infusion increased wedge mean pressure and left atrial pressure (LAP) significantly more than it did right atrial pressure. The values for WMP, LAP and RAP had all declined substantially two hours after the end of the dextran infusion.

and left atrial pressure were essentially equal in these studies. Thus the general validity of the well-placed Swan-Ganz catheter as a guide to left atrial pressure was reaffirmed.

The most significant finding, in comparing right atrial and left atrial pressures in the presence of increasing fluid overload, was that the rise in directly measured left atrial pressure *invariably* exceeded the rise in right atrial pressure. The difference between maximum right atrial pressure and maximum left atrial pressure averaged 10.8 mm Hg. This difference was statistically significant ($p < .001$). Furthermore, a number of dogs exhibited various degrees of pulmonary edema, manifested by the discharge of frothy fluid from the endotracheal tube. Clearly, acute fluid overload and pulmonary edema can be produced by rapid and excessive colloid infusion in the absence of a marked rise in right atrial pressure, a matter of considerable clinical importance.

Hypertension Caused by Dextran Overload

A second finding of much clinical interest was that the colloid fluid overload, expected by the rapid infusion of dextran, produced a rise in systemic arterial blood pressure in all dogs so studied. We plan later to re-examine this relationship in additional dogs using blood transfusion instead of dextran, but indicative data have already been reported by Guyton.[1] Thus, it appears likely that excessive blood volume may be one cause of the temporary hypertension at times observed in the recovery room following substantial blood transfusion. The rise in systemic arterial pressure, which occurred in all dogs, was statistically significant at one hour following the infusion ($p < .005$).

Intermittent Positive Pressure Ventilation

Many workers have documented the effects of intermittent positive pressure ventilation upon pressures in the several cardiac chambers. In brief, ventilation at 20 cm H_2O had a statistically significant effect upon right atrial, left atrial, and wedge pressures. Ventilation at 30 cm H_2O had a still greater effect on these pressures. Forty centimeters of H_2O intermittent positive pressure ventilation increased right atrial pressure to twice the control level and wedge pressure to three times the control level (Fig. 3). Systemic arterial pressure was moderately diminished by these levels of positive pressure pulmonary ventilation.

These findings support the usual practice of disconnecting the patient from the ventilator while right atrial, left atrial and wedge pressures are being taken.

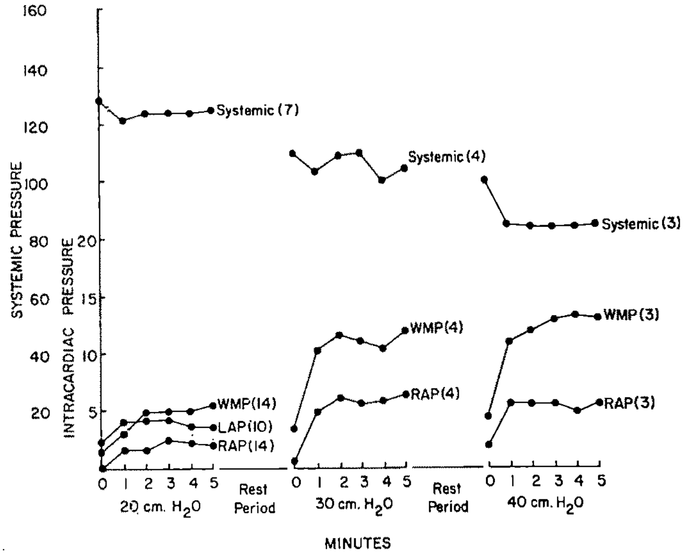

FIG. 3. Effect of positive pressure ventilation on systemic and intracardiac pressures. As positive pressure ventilation was increased from 20 cm H_2O to 40 cm H_2O, there was a progressive rise in wedge mean pressure (WMP), left atrial pressure (LAP) and right atrial pressure (RAP). Systemic arterial pressure progressively declined. The numerals in parentheses reflect the number of animals whose data were used in constructing the given curves.

Discussion

The increasingly widespread awareness of the relatively huge losses of blood and other body fluids which may occur in association with surgical injury has led to serious and at times fatal excesses in the administration of blood and electrolyte fluid to surgical patients. Extending the work of Moyer[2] in burns, Shires *et al.*[3] reported an improved dog survival rate when simple blood loss shock was treated with Ringer's lactate in addition to replacement of the shed blood. Shires cautioned against excessive use of Ringer's lactate, or "white blood" as it was often called, but it became commonplace for the patient undergoing a routine gastrectomy or aneurysm resection to receive several liters of electrolyte solution while on the operating table. To be sure, no harm was done in most instances, but in the occasional patient who exhibited oliguria postoperatively the renal management was at once complicated by this initial fluid overload. Moreover, in the patient with limited respiratory reserve, the increase in pulmonary water posed the hazard of a diffusion defect with the threat of a diminished P_{O_2} and at times an elevated P_{CO_2}. Finally, many patients who had received generous blood and fluid administration, far in excess of probable losses, exhibited a substantial systemic arterial hypertension postoperatively, at times requiring an anti-hypertensive agent to reduce the blood pressure and diminish the risk of intracranial hemorrhage.

The intermittent monitoring of central venous pressure as a guide to fluid replacement was emphasized by Wilson in 1962. This modality did much for the accurate replacement of blood in many patients, but it was soon apparent that in the presence of certain pulmonary diseases, and in mitral or aortic valve disease, and following complete repair of tetralogy of Fallot, to name a few circumstances, the measurement of only right atrial or central venous pressure afforded inadequate information upon which to base blood replacement: left atrial pressure measurements were also required, in addition to systemic arterial blood pressure, rate of urine output, pulse rate, and general appearance of the patient. Furthermore, it was not always remembered that, in contrast to a colloid solution such as blood or plasma or dextran, the electrolyte solution might be given in serious excess without producing a marked rise in the central venous pressure. Central venous pressure measurements were a better guide for the replacement of blood and other colloid solutions which tend to increase blood volume per se, than a guide to replacement of electrolyte containing fluids which increased blood volume only indirectly by increasing intracellular fluid volume.

When in open-heart surgery it was found that central venous pressure measurements alone gave inadequate information upon which to base blood replacement in the postoperative period, it became common practice to leave a small catheter in the left atrium, to permit monitoring of left atrial pressure. Later, the Swan-Ganz[4] catheter was developed, by means of which the pulmonary wedge pressure could be measured at the bedside. The pulmonary wedge pressure, obtained by passing the catheter from a peripheral vein through the right heart and far out into a small branch of the pulmonary artery, closely approximates the left atrial pressure. Furthermore, in the absence of mitral valve disease, the left atrial pressure may closely approximate the left ventricular end-diastolic pressure. Thus, a reduced pulmonary wedge pressure in the presence of systemic arterial hypotension would suggest the need for blood transfusion. In the absence of pericardial tamponade, an *elevated* wedge pressure in the presence of systemic arterial hypotension, would suggest the need for digitalis or other cardiotonic drugs to improve left ventricular function.

The studies reported here are to be followed by investigations of hemorrhagic shock in which simple replacement of shed blood is compared with replacement of shed blood plus Ringer's lactate solution equal to five per cent of the body weight of the dog. However, the data presented have considerable clinical importance. Dextran overload increased left atrial pressure more than right atrial pressure. Thus, pulmonary overload and pulmonary edema could develop before right atrial or central venous pressure had risen to an alarming degree. Left atrial pressures are seen to be most useful in preventing pulmonary overload when a large volume of colloid solution is being administered rapidly. Also of interest, a norepinephrine drip increased left atrial pressure more than it did right atrial pressure. Finally, positive pressure ventilation was seen to increase both right and left atrial pressures, and to lower systemic arterial pressure at the ventilatory pressures employed.

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Chemotherapy of Malignant Melanoma with Dimethyl Triazeno Imidazole Carboxamide (DITC) and Nitrosourea Derivatives (BCNU, CCNU)

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Chemotherapy for metastatic melanoma was performed in 80 consecutive evaluable patients. DTIC, BCNU and CCNU produced responses in 28% of patients, alone or in combination with each other. Three of 62 patients treated with DTIC remain free of tumor, off therapy at 18–36 months following objective regression of metastases. Chemotherapy with commercially available drugs continued to be uniformly unsuccessful. DTIC was used successfully in treatment of extensive extracranial disease, including one patient with metastatic melanoma during pregnancy. Cerebral metastases were the sole or major cause of death in 8/9 patients who relapsed following control with DTIC for nine months or longer, and one patient developed a carcinoma of the breast following therapy with DTIC and BCNU. Remission was induced in two patients with intralesional BCG, after prior attempts to control metastases with DTIC and combination chemotherapy.

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THE OPTIMUM MANAGEMENT of malignant melanoma is a problem which has perplexed surgeons for more than a century. Theodor Billroth described the fatal course of three patients whom he operated upon between 1860 and 1876, and commented that even the histology of melanoma was puzzling; "I scarcely know whether to classify these tumours as sarcomata or carcinoma . . . which occur in the form of small, dark, nodules, and fungus-like growths in the skin. . . . However, I am inclined to consider them as sarcomata, since the new formation invariably arises in the papillary layer of the cutis."[1]

At present, approximately 8,450 new cases of melanoma occur annually in the United States. Twenty per cent of these patients present with disseminated disease, which is with rare exception always fatal. Of the 5,600 who are first seen with localized disease, only 58% are alive at ten years, and for those who present with regional metastases, the ten-year survival is only 27%.[3,6]

Surgical management has evolved into an aggressive attack, with wide local excision being used to remove the primary tumor. Regional node dissection is usually performed when nodes are palpable or enlarged, but not fixed or matted together.[11] "Prophylactic" regional node dissection[23,32] has declined somewhat in recent years, especially for melanomas of the lower extremity. Reports of spontaneous remissions[8] and autoimmunity[7,15,30] to melanoma have provoked many studies of immunotherapy, using specific and nonspecific methods, active and passive induction, and cellular and humoral antibodies.[24,27]

Chemotherapy for metastatic melanoma has also been widely employed, but the results have generally been unimpressive until recently. Commercially available antineoplastic agents have not provided satisfactory results, except in occasional patients, or for short periods of time.[20] An exception to this uniformly poor situation is the higher percentage of responses reported from limb perfusion with a variety of drugs, particularly phenyla-

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Copies of COG Protocols 7130 and 7040 may be obtained for reference from the Central Oncology Group Statistical Office, University of Wisconsin School of Medicine, Madison, 53715.

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lanine mustard. Krementz and Creech reported control of metastatic or recurrent melanoma for five years in 33% (23/70) of patients with limb perfusion.[18] A significant improvement in systemic chemotherapy of melanoma was subsequently reported in studies with dimethyl triazeno imidazole carboxamide (DTIC, NSC 45388),[21] a finding which was later confirmed by other investigators and cooperative groups.[9,25,33] When the nitrosourea BCNU (NSC 409962) became available, additional successes in chemotherapy of melanoma were reported.[29] Subsequently, another nitrosourea, CCNU (NSC 79037), has been made available for clinical trials.[10]

This report supplements our previous report[19] and summarizes six years of experience with chemotherapy for malignant melanoma. The present report gives the results of therapy with chemotherapeutic agents which presently appear to be of greatest benefit, DTIC, CCNU and BCNU. The quality and duration of responses to therapy are outlined, and the current investigative programs for combination chemotherapy are described.

Materials and Methods

This report is based upon 80 consecutive evaluable patients with metastatic melanoma treated by the authors between 1968–73. These patients are among 87 patients with melanoma and 663 patients with other neoplasms who were referred for therapy during this five year period. All of the 80 evaluable cases were treated with chemotherapy alone at this time, having failed on prior surgical therapy or having first been seen at a time when widespread metastatic melanoma was present.

The principles of patient selection and methods of objective evaluation were described previously.[13,14,16,17] Briefly, partial response (PR) was defined as a 50% decrease in cross-sectional area of at least one measured tumor mass, without simultaneous progression in any other mass, or any worsening of the patient's general condition. Complete response (CR) was defined as complete disappearance of all tumor masses, and of all signs and symptoms related to tumors.

Our previous report[12] described a total lack of response in 22 courses of chemotherapy with conventional drugs in 12 patients with malignant melanoma. The present report summarizes the results of therapy with DTIC, BCNU, and CCNU (Fig. 1) alone, in sequence, or in combination. Therapy was given using DTIC in 62 patients, BCNU in 18 patients, CCNU in six patients, and combinations of these drugs were given to nine patients. Fifteen patients received sequential therapy with one or more of the drugs. DTIC was usually selected as the first agent for chemotherapy except when signs of cerebral metastases were present. Recently, however, COG protocol 7130 has been utilized as a randomized, prospective comparison of the effect of DTIC alone with the drug combinations outlined in the next paragraph. This protocol also provides a cross-over randomization, permitting administration of one of the three drug combinations to patients previously treated with DTIC alone.

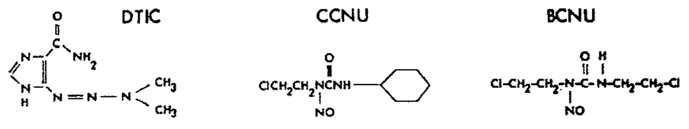

FIG. 1. Structural formulas of the drugs DTIC [(5-(3,3 dimethyl-1-triazeno) imidazole-4-carboxamide, (NSC 45388)], CCNU [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, (NSC 79037)] and BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea (NSC-409962].

DTIC was administered by rapid intravenous injection at a dose of 4.5 mg/kg/day for 10 days, repeated at 6–8 week intervals. BCNU was given as a slow intravenous injection at a dose of 1.5 mg/kg/day for five days. CCNU was given as a single oral dose of 130 mg/M^2. BCNU and CCNU were repeated at 8–12 week intervals. Combinations of these agents and vincristine (VCR) or hydroxyurea (HYD) were administered as described in Protocol 7130 of the Central Oncology Group (COG):

DTIC	2.7 mg/kg I.V. days 1–5
CCNU	1.5 mg/m^2 P.O. day 2
VCR	0.027 mg/kg I.V. days 1,5

or

DTIC	2.7 mg/kg I.V. days 1–5
BCNU	2.0 mg/m^2 I.V. day 2
VCR	0.027 mg/kg I.V. days 1,5

or

DTIC	2.7 mg/kg I.V. days 1–5
BCNU	2.0 mg/m^2 P.O. day 2
HYD	20 mg/kg P.O. days 2, 5, 9, 12, 16, 19

Dosages were based on the lesser of ideal or actual body weight. Therapy was withheld and dosages reduced when necessary because of toxicity, according to previously established guidelines (COG Protocol 7130). Therapy was continued until symptoms or signs of tumor progression occurred. The combination of DTIC, BCNU and VCR has been described previously,[22] although the present study utilized somewhat lower doses.

Seven of the 87 patients with melanoma who were referred for therapy are not considered evaluable at this time, because they had no known tumor present at the time of their referral. They were patients with recently resected melanoma who were in poor prognostic categories. These seven patients were entered into a national cooperative surgical adjuvant study (COG Protocol 7040). This is a randomized prospective study which is offered to selected patients with poor prognosis, including Stage I (localized) melanoma in unusual sites[5] and

TABLE 1. *Results of Chemotherapy for Melanoma in 80 Patients**

Agent	Number of Patients	Responses† Partial	Complete	Total
DTIC	62	10	8	18
BCNU	18	2	1	3
CCNU	6	2	0	2
Combination	9	0	1	1
Total		14	10	24

* 65 patients were treated with only one agent or one combination; 15 patients were treated in sequence with more then one agent or combination.

† 24 responses occurred in 23 patients. One patient responded to sequential therapy with both DTIC and BCNU.

TABLE 2. *Cross-over Effects in Chemotherapy for Melanoma*

Number of Patients	First Drug	Second Drug
3	*BCNU*	*DTIC*
	1 responder 2 non-responders	3 non-responders
2	*Combination*	*DTIC*
	2 non-responders	2 non-responders
6	*DTIC*	*BCNU*
	1 non-responders 1 responder	2 responders
	1 responder 3 non-responders	4 non-responders
4	*DTIC*	*Combination*
	1 responder 2 non-responders	3 non-responders
	1 non-responder	1 responder
15		

Stage I melanoma of the trunk, ear, sole, palm, and subungual areas; Stage II (lymph nodes), and Stage III (solitary distant metastases). Patients randomized for therapy received four courses of DTIC in the second to eleventh months following resection of all known tumor. Three patients were randomized for immediate postoperative chemotherapy with DTIC. The other four patients were randomized for treatment with surgical resection alone, followed by observation at regular intervals.

Patients who failed to respond to chemotherapy with DTIC and the nitrosoureas, or who relapsed after temporary response, were subsequently treated with other experimental agents or conventional drugs, and in some instances by additional surgery or radiation therapy.

Results

Twenty-three (28%) of the 80 evaluable patients responded to treatment with DTIC or the nitrosoureas, alone or in combination (Table 1). Fifteen patients were later treated in sequence with another of these agents or combinations, and one of these 15 patients responded to both the first and second therapies (Table 2).

DTIC Alone

Objective responses were produced by DTIC in 29% (18) of 62 patients treated with this drug as a single agent (Table 3 and Fig. 2). Eight patients exhibited complete response (CR) and ten patients exhibited partial response (PR). Duration of CR varied from three months to 36+ months. Three patients remained in CR for more

TABLE 3. *Responses to DTIC*

Patient No.	Age	Sex	Primary Site	Metastatic Sites	Response	Duration	Status
1.	52	M	Skin, back	Nodes neck, bilateral	CR	30 months	Alive and well, free of disease
2.	22	F	Skin, back	Axilla, recurrent nodes	CR	27 months	Alive and well, free of disease
3.	49	F	Skin, leg	Lung, status postresection of cecal and cutaneous metastases	CR	12 months	Alive and well, free of disease
4.	42	M	Skin, leg	Skin, disseminated	CR	19 months	Died, cerebral and other metastases
5.	28	M	Skin, thorax	Lungs, liver, skin, recurrent axillary nodes	CR	11 months	Died, cerebral metastases
6.	62	F	Skin, back	Skin, lung	CR	9 months	Died, cerebral metastases
7.	57	F	Vulva	Skin, lung	CR	4 months	Died, cerebral metastases
8.	43	M	Skin, back	Nodes neck and axillae, bilateral	CR	3 months	Died, cerebral metastases
9.	28	F	Skin, leg	Lung, breasts, abdomen, recurrent groin nodes. Pregnant	PR	10 months	Died, cerebral and other metastases
10.	63	F	Skin, leg	Liver, groin nodes	PR	9 months	Died, progressive recurrence
11.	53	M	Skin, ear	Lung	PR	9 months	Died, cerebral and other metastases
12.	42	F	Skin, arm	Satellitosis and neck node	PR	8 months	Relapsed; subsequently free of disease with BCNU and BCG
13.	58	F	Eye	Liver	PR	2 months	Died of progressive recurrence
14.	62	F	Unknown	Groin, axillary metastases	PR	2 months	Died of peritoneal metastases
15.	36	F	Skin, back	Lungs	PR	1 month	Died of progressive recurrence
16.	61	M	Skin, leg	Groin nodes	PR	1 month	Died, cerebral and other metastases
17.	41	M	Skin, groin	Groin and peritoneal metastases	PR	1 month	Died of progressive recurrence
18.	44	M	Skin, thigh	Groin nodes and multiple recurrence	PR	1 month	Entire area re-excised, alive and well, and now free of disease 2 years

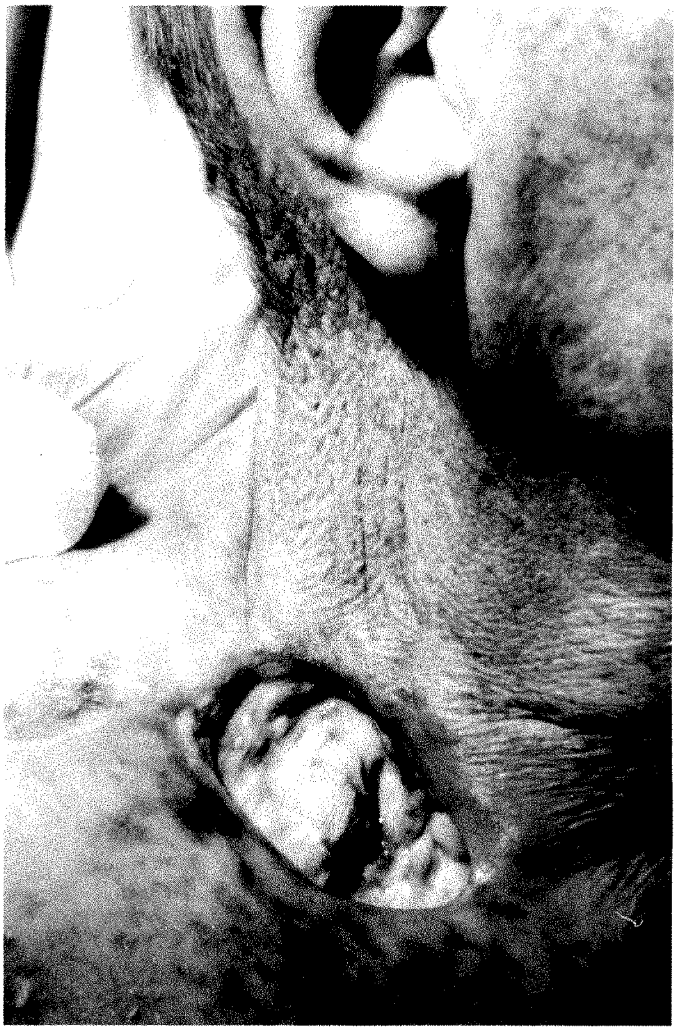

FIG. 2. Recurrent metastatic malignant melanoma in right supraclavicular fossa. Brachial plexus palsy, severe causalgia, and a 3 × 3 cm metastatic left mid-cervical lymph node were present. FIG. 2a. (above) Prior to therapy (May 1970). FIG. 2b. (next page) Improvement in right supraclavicular area following first three courses of DTIC. Left cervical node regressed completely during first 10 days of therapy. Pain in right neck and arm gradually decreased as tumor regressed and wound healed (December 1970). FIG. 2c. (next page) Continued improvement following two more courses of DTIC. Pain is nearly gone (September 1971). Patient remains free of new recurrence or metastases, works full time, uses small amounts of pain medication and diuretics for arm edema. Refused skin graft to cover small area of residual granulations (June 1973).

than 12 months (Karnovsky Category I-C), and are now off therapy. Six other patients were in CR or PR, with subjective improvement, for nine months or longer (Karnovsky Category I-B). Of the nine patients in category I-B who have subsequently died, the relapse was due to cerebral metastases in eight cases. In 6/8 of these patients the noncerebral metastatic disease remained in complete or partial remission at the time of progression of CNS metastases. Additional courses of DTIC were administered to all 18 responders, with five courses being given to patients in response for 12 months or longer. None of the five patients in whom DTIC was used as a second agent responded to DTIC therapy (Table 2). Toxicity was assessed in detail in the first 50 patients treated (Table 4). It consisted of mild to moderate leukopenia, thrombocytopenia, nausea and vomiting, and was not life endangering or permanent.

Nitrosourea Alone

BCNU alone produced CR in one patient and PR in two patients out of 18 patients treated (Fig. 3). The patient with CR has continued to remain free of melanoma for 34 months, although she has subsequently developed extensive carcinoma of the breast. It should be noted that she received one course of DTIC, without improvement, prior to her first course of BCNU. One patient with temporary PR was subsequently rendered free of disease for 18+ months by resection and intralesional injections of BCG. The patient had also been treated previously by DTIC, and had a PR with DTIC therapy (Table 3, Patient 12).

CCNU alone produced PR in 2/6 patients, both of whom have subsequently relapsed and died. Definite improvement in signs and symptoms of cerebral metastatic disease occurred temporarily in one patient with CCNU and one with BCNU.

The three patients with CR from DTIC lasting more than 12 months were advised to receive CCNU or BCNU because of the apparent beneficial effects of these agents on cerebral metastases, and because of the high incidence of relapse due to cerebral metastases seen after therapy with DTIC alone. One patient accepted BCNU,

TABLE 4. *DTIC Toxicity*
(50 Consecutive Patients)

	Number of Patients	Percent of Patients
Leukopenia		
minimal (WBC reduced 1,000 or more cells/cmm from initial value)	33	66%
moderate (WBC reduced 2,000 or more cells/cmm from initial value)	22	44%
severe (WBC reduced to 3,200 cells or less/cmm)	3	6%
Thrombocytopenia		
minimal (platelets reduced 100,000 or more cells/cmm from initial value)	24	48%
moderate (platelets reduced 200,000 or more cells/cmm from initial value)	14	28%
severe (platelets reduced to less than 75,000/cmm	10	20%
Time of change of blood counts:		
WBC nadir (mean) 3 weeks		
WBC recovery (mean) 4 weeks		
Platelet nadir (mean) 4 weeks		
Platelet recovery (mean) 6 weeks		
Hematocrit reduction > 5% vol.	3	6%
Nausea and vomiting for 3–4 days	37	74%
Flu-like syndrome at 6–7 days	3	6%

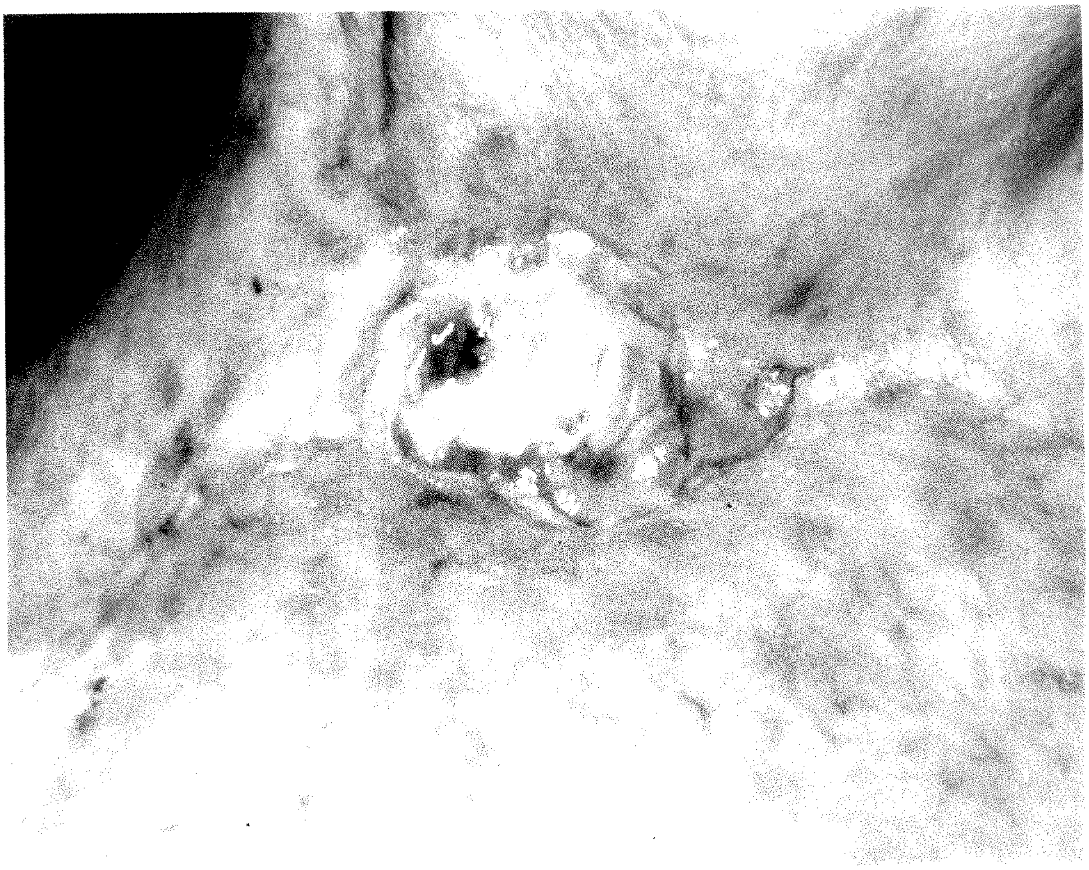

Fig. 2b.

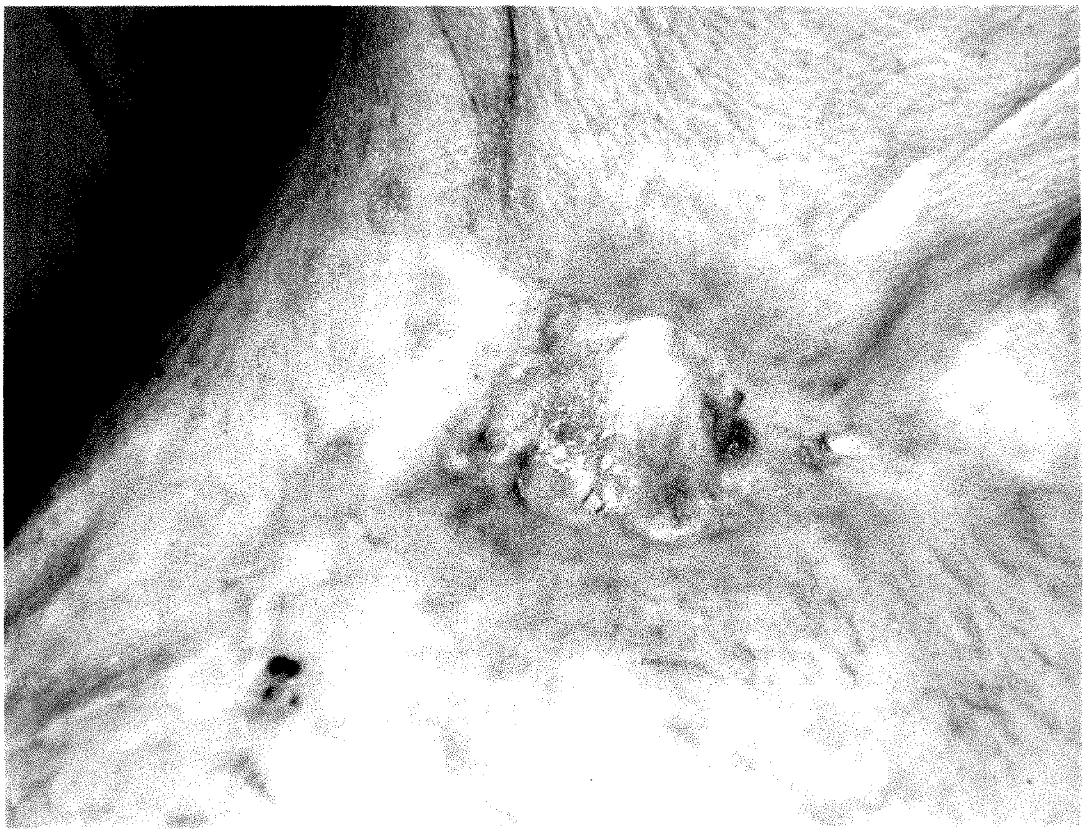

Fig. 2c.

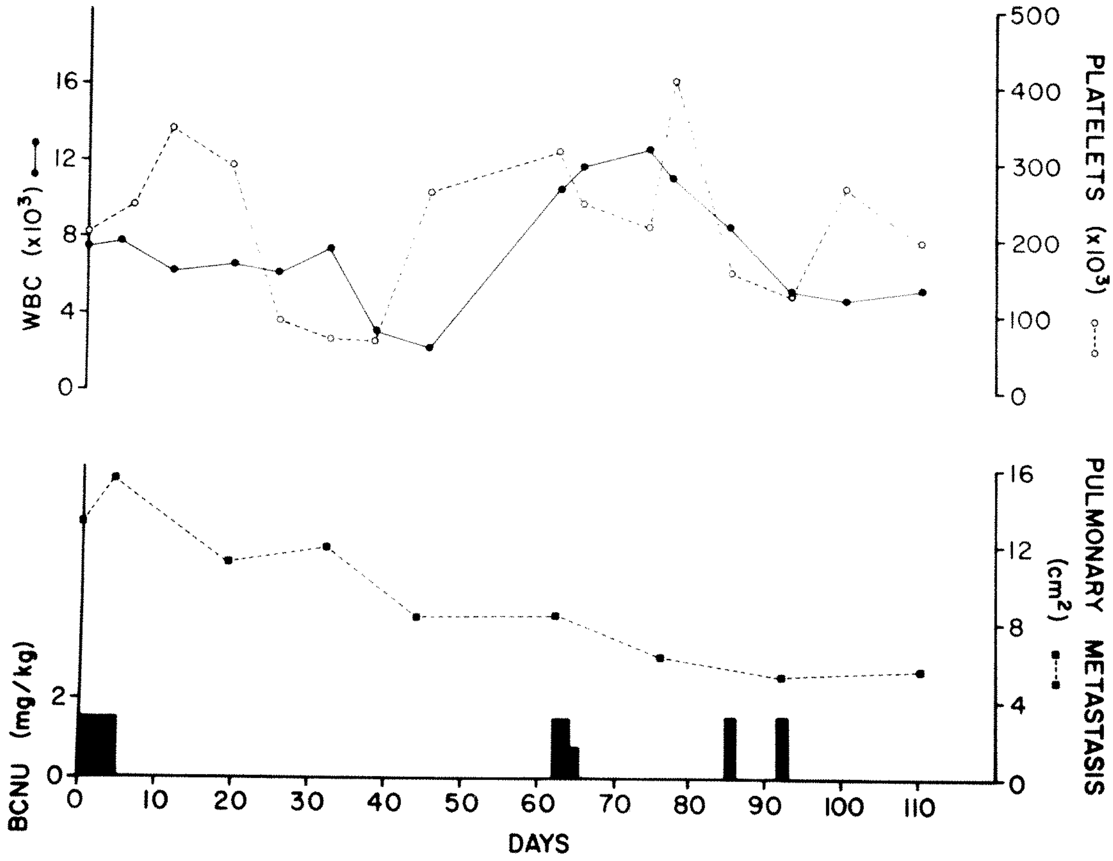

FIG. 3. BCNU therapy of metastatic melanoma: Partial response. Pulmonary metastasis 3.8 × 3.5 cm (13.3 cm²) decreased to 2.5 × 2.3 cm (5.75 cm²) by day 110. BCNU 1.5 mg/kg/d × 5 caused leukopenia (nadir 2,200 at day 46) and thrombocytopenia (nadir 63,000 at day 39). BCNU doses were accordingly reduced in subsequent therapy, and did not produce complete regression of metastasis. Therapy with BCNU was therefore discontinued after 110 days.

another CCNU, and the third declined further treatment, but all three have thus far remained in good health.

Combinations

Combinations of DTIC and BCNU or CCNU were administered to nine patients, one of whom had an objective response (CR). Transient objective and subjective improvement occurred in 2/5 patients who received DTIC, BCNU and VCR, but of insufficient duration to be classified as PR. Progression occurred in the one patient treated with DTIC, CCNU and VCR. The combination of DTIC, BCNU and HYD produced a CR in one of three patients treated. After a response lasting for nine months, this patient then developed progressive, fatal cerebral metastases.

Crossover Effects (Table 2)

In 15 patients it was possible to assess the effects of therapy with one or more of the three agents, DTIC, BCNU or CCNU, on subsequent response to other therapy. Three patients received DTIC after prior BCNU therapy. One had a prior PR to BCNU; none subsequently responded to DTIC. Two other patients failed to respond to DTIC after prior unsuccessful therapy with combinations. On the other hand, one patient who failed to respond to DTIC later had a CR for nine months when treated with DTIC, BCNU and HYD. Three other patients were treated unsuccessfully with combinations after prior therapy with DTIC. In one of the cases DTIC had been effective, and in the other two it had been ineffective. One of the latter two patients subsequently had a complete regression (for 18+ months) of widespread satellites of melanoma located on the thigh, popliteal space, groin and buttock, following administration of bacillus Calmette Guerin (BCG). This patient had failed to respond to DTIC, then DTIC, BCNU and HYD, and then a prolonged course of 5FU, cyclophosphamide, prednisone, VCR and methotrexate. Nevertheless, he developed regression of all injected and uninjected lesions during a six month course of intralesional injections with Tice-strain BCG, given in doses of .05–0.5 cc every 1–4 weeks. One patient has had a CR with BCNU after prior unsuccessful therapy with DTIC. Five other patients were treated with BCNU alone after prior therapy with DTIC. Two of these patients had a prior response to DTIC, and one of these subsequently responded to BCNU, and later to BCG.

Adjuvant Therapy

None of the seven patients in the randomized adjuvant study has been lost to followup; two have relapsed and the others are free of tumor at periods ranging from 3 to

18 months. Four were randomized for observation and three for postoperative therapy with DTIC. The results of the study will be presented in detail when the findings are statistically valid.

Other Therapy

Most of the patients who failed to respond to DTIC or the nitrosoureas were subsequently treated with a variety of commercially available chemotherapeutic agents, other experimental drugs or combinations. Palliative local irradiation therapy was used in five patients, and six patients received intralesional or tine-injected BCG. Resection of solitary metastases were performed for palliation in three cases.

Responses were rarely observed to other agents or combinations, and none has been complete or prolonged, except with BCG, which produced the two remissions described above. Betatron therapy has completely controlled satellitosis of the skin in one patient for four years, and the three patients who were reoperated upon were again rendered free of tumor for periods of six months to three years.

Discussion

The variable natural history of melanoma and the apparent capricious responsiveness of this type of tumor to drug therapy has produced wide-spread skepticism regarding new reports of success with chemotherapy. The authors of the present study were unable[12] to confirm the promising reports of others with various agents prior to 1968, when DTIC and the nitrosoureas became available.[19] Although other systemic agents have apparently been effective in some instances, the responses are usually short-lived and of little overall significance to the patients.

The situation is now apparently different, for DTIC and nitrosoureas produced responses in approximately 28% of our 80 evaluable patients. The imidazole carboxamide derivative DTIC was the agent which produced the largest number of responses, and the most useful palliation. This drug produced responses in approximately 29% of patients treated. The responses were not limited to patients with minimal or asymptomatic disease (Table 3). Extensive morbidity was controlled and preterminal patients were restored to health for periods of several months to years. In one case (Table 1, #9) treatment was successfully carried out with DTIC beginning in the second trimester of pregnancy, and although the patient subsequently relapsed, her child is now well at the age of three years. In another case (Table 1, #1), severe causalgia due to metastases to the brachial plexus was controlled with DTIC and the patient remains free of tumor three years later. Extensive skin, pulmonary, hepatic, soft tissue, abdominal, lymph node and breast metastases have regressed temporarily or permanently in the responding patients. Responses to the nitrosoureas and various drug combinations occurred less frequently (18%), but three of the six responses to nitrosoureas and combinations occurred after previous treatment had been given with DTIC, and in two of these cases the tumor had been unresponsive to DTIC therapy.

This study raises many questions which cannot be answered by the present investigation. These questions include the problem of predictability of response: amelanotic lesions and cerebral metastases have not yet responded to DTIC in our experience. On the other hand, neither age, location of other metastases, or duration of illness appeared to have any apparent effect on subsequent responsiveness to DTIC or nitrosoureas. The occurrence of carcinoma of the breast *de novo* in a patient who previously had been treated with DTIC and BCNU raises the question of carcinogenesis of these agents, a problem anticipated because of previous studies with DTIC in rats.[31] This patient is only the second in our entire group of 750 patients treated with cancer chemotherapy who developed a second primary neoplasm (the other patient died of pancreatic carcinoma after four years of cyclophosphamide therapy for lymphocytic lymphosarcoma).

The problem of cerebral metastases also is a significant consideration in patients who respond to chemotherapy with DTIC. It is unknown whether cerebral metastases are a problem as a result of failure of DTIC to enter the brain, or because of the relative immunological sanctuary of the central nervous system with respect to tumor growth, or for other reasons. The possibility of using DTIC or other agents intrathecally must eventually be considered, in spite of the theoretical biochemical necessity which has proposed for activation of the drug by the liver.[34]

The effect of DTIC and the nitrosoureas on the immunological response to tumor antigens must receive greater attention in future studies. Preliminary reports of immunologic depression from DTIC[26] have not been confirmed in subsequent studies,[4] but these studies are obviously incomplete at present. DTIC has been reported to produce both immunosuppression and stimulation of tumor allograft antigenicity in mice bearing transplanted leukemia.[2] Increased immunogenicity of other experimental tumors has been ascribed to another imidazole carboxamide derivative PCA (pyrazole-4-carboxamide, 3 (or 3)-amino).[28]

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Primary Malignancies of the Small Bowel:

A Report of 96 Cases and Review of the Literature

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The clinical records and histologic sections of 96 cases of primary small bowel malignancies (excluding lymphomas and periamullary lesions) were reviewed. The location, clinical presentation, pathologic findings, treatment and outcome are compared to the collected published experience, approximately 2400 cases. There were 48 adenocarcinomas, 37 carcinoids, and 11 leiomyosarcomas. Fifty-one men and 45 women ranged from 31 to 83 years old. Eighty-four caused symptoms leading to operative diagnosis; 12 carcinoids were incidental autopsy findings. The most common presentation was pain (33%) followed by weight loss (23%) obstruction (16%), hemorrhage (15%), jaundice (5%), intussusception (3%) and perforation (3%). Masses were felt in 30% of the cases, but were usually dilated bowel or intussusception rather than the tumor *per se*. Curative resection was attempted in 80 of 84 operatively diagnosed tumors. The 80% mortality among patients followed 5 years is attributed to the late appearance of symptoms and anatomic obstacles to a truly radical operation.

PRIMARY MALIGNANT TUMORS of the small bowel are relatively uncommon neoplasms. A duodenal carcinoma described by Hamburger[19] in 1746 seems to be the earliest recorded example, and the first review of the subject was by Leichtenstein[24] in 1876. Subsequently, approximately 2400 cases have been reported in the major reviews of these tumors. Rochlin and Longmire[44] estimated that malignancy was 40 to 60 times more common in the colon than in the small intestine. McPeak[30] found only 84 small bowel cancers in 137,000 admissions to a cancer hospital and Eckel found only 12 cases in 500,000 admissions to this institution between 1932 and 1948. We have reviewed the records of The New York Hospital-Cornell Medical Center for period 1932–1972, and, including the 12 cases previously reported by Eckel, found 96 primary malignant tumors of the small intestine. During the same period there were 84 benign tumors. The diagnosis was confirmed histologically in all lesions included in this study. Twenty-five lymphomas were not included, but have been reported previously.[26] This report also excludes lesions of the ileocecal valve and the Ampulla of Vater. The tumors included: 48 adenocarcinomas, 37 carcinoids, and 11 leiomyosarcomas (Table 1). We are comparing our experience with these tumors with that reported in previous studies.

Clinical Presentation

Approximately equal numbers of males (51) and females (45) were affected in contrast to a definite male predominance reported by others.[34,38,42,47] The age range was 31 to 83 years, with an average of 53. The peak incidence of adenocarcinomas was in the seventh decade, while carcinoids and leiomyosarcomas were more frequent in the sixth decade. This experience is similar to that of others.[4,44] Only seven instances of malignant small intestinal tumors in patients younger than 30 are reported.

Eighty-three (88%) of the tumors caused symptoms and were diagnosed at operation. Twelve tumors, all carcinoids, were incidental findings at autopsy. Duration and character of symptoms varied somewhat with tumor type and location. The average duration of symptoms of adenocarcinoma was 6 months; leiomysarcomas, 8 months,

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TABLE 1. *Distribution of Malignant Tumors of Small Intestine*

	Total	Duodenum	Jejunum	Ileum	Meckel's
		96 New York Hospital Cases			
Adenocarcinoma	48	19 (40%)	16 (33%)	13 (27%)	—
Carcinoid	37	11 (29%)	1 (3%)	25 (66%)	1
Leiomyosarcoma	11	—	4 (36%)	7 (64%)	—
		2144 Collected Cases			
Adenocarcinoma	1002	399 (40%)	381 (38%)	221 (22%)	1
Carcinoid	714	42 (5%)	73 (10%)	594 (84%)	5
Leiomyosarcoma	421	41 (10%)	156 (37%)	224 (53%)	—
Other Sarcomas	7	2	—	5	—

and carcinoids, 12 months. These findings are similar to earlier reports.[20,22,38,39,42] Generally, duration of symptoms was longer with the more distal lesions, which may reflect the greater proportion of more slowly growing carcinoids in the ileum.

The symptoms associated with malignant tumors of small intestine are summarized in Table 2.

Pain

Thirty-two patients (33%) complained of pain which was the most common symptom in our cases and also in several other reports.[14,21,39,46] The character of pain was quite variable including epigastric burning, cramps, dull aches, etc. However, the incidence of pain as recorded in other reviews was quite variable, ranging from only 14%[1] to as much as 86%.[48]

Weight Loss

Twenty-two (23%) patients reported weight loss, averaging 23 pounds. Weight loss is a very commonly reported symptom, the incidence ranging from 32%[46] to 67%[56] in other reports.

Obstruction (Including Intussusception)

Obstruction occurred in 15 patients (16%) and was manifested as intussusception in three instances. Although primary tumors have been estimated to be responsible for only 1.5% of small bowel obstructions,[29] intermittent partial obstruction has been regarded as the most characteristic evidence of malignancy in the small intestine.[31] The reported incidence of obstruction ranges from 5%[12] to 38%.[46] We calculate that approximately 5% of 254 reported instances of obstructing malignant tumors of small bowel are due to intussusception.

Obstruction is more characteristic of carcinomas than sarcomas. This is because the former grow in an annular constricting fashion whereas the latter compress the lumen only after reaching a large size. Polypoid adenocarcinomas are the most likely lesion to initiate intussusception, which also may rarely be due to carcinoids.[7]

Hemorrhage

Fourteen patients (15%) had evidence of gross or occult bleeding. The reported evidence of hemorrhage ranges from 3%[14] to 76%.[38] Massive hemorrhage is the dramatic presenting symptom of some leiomyosarcomas, and bleeding is relatively more common with that tumor than with adenocarcinomas.[20,53] Carcinoids rarely cause hemorrhage.[7,34]

Mass

A palpable mass was recorded in 29 patients (30%). Since many of the tumors were relatively small, the palpable lesion in some instances was undoubtedly not the tumor itself but dilated intestine or an intussusception. Masses associated with jejunal tumors were generally in the left upper quadrant, while those associated with ileal lesion were in the lower abdomen. In other reports the incidence of palpable masses range from 7%[14] to 63%.[44]

TABLE 2. *Clinical Manifestations*

	New York Hospital Cases				Collected Cases
	48 Adenocarcinoma	37 Carcinoids	11 Leiomyosarcomas	96 Total %	808 Total
Pain	20	4	8	32 (33%)	20%
Weight Loss	11	9	2	22 (23%)	39%
Hemorrhage	6	5	3	14 (15%)	23%
Obstruction	5	6	1	13 (14%)	30%
Jaundice	5	—	—	5 (5%)	2%
Intussusception	2	1	1	4 (4%)	1%
Perforation	1	—	2	3 (3%)	4%

Jaundice

Small bowel tumors, except for periampullary lesions, rarely cause jaundice. Icterus was observed in five patients (5%), all with adenocarcinoma involving the second portion of the duodenum. The incidence of jaundice in the literature ranges from 2.5%[39] to 14%.[14]

Perforation

Only three patients (3%) had perforation. All were ileal tumors, two leiomyosarcomas and one adenocarcinoma. The reported incidence of perforation ranges from 0%[14] to 14%.[7]

The diagnosis of malignant tumors of the small bowel is usually made only after the symptoms of advanced disease have developed. In many patients, the first symptoms as epigastric burning or post-prandial discomfort may be treated for a time without a definite diagnosis. Hancock[20] reported that over half of his patients with cancers of small bowel were initially labeled neurotic. Physical findings are also usually not present until disease is advanced, and even then may be absent in many patients. It is, therefore, not surprising that a definite diagnosis of a small bowel tumor was made pre-operatively in only 30 (35%) of the 84 patients with tumors diagnosed in life. Other authors have reported correct pre-operative diagnosis in 17%[4] to 52%[41] of their cases. In most instances a correct pre-operative diagnosis was accomplished by roentgenograms of the small intestine.[3,7,28]

The possibility of a neoplasm should be suspected in any patient with obstruction or bleeding of undertain etiology. Duodenal tumor should be considered when there is duodenal ulcer with achlorhydria or ulceration outside of the bulb.

Pathologic Findings

The principal primary malignant tumors of small intestine, in descending order of frequency, are: adenocarcinomas (50%), carcinoids (39%) and leiomyosarcomas (11%). In 2144 previously reported cases, there were 1050 adenocarcinomas (47%), 715 carcinoids (33%), 421 leiomyosarcomas (19%) and 7 other malignant tumors. In our experience primary lymphomas were less frequent than adenocarcinomas but more common than leiomyosarcomas. Lymphomas have often been excluded from studies of intestinal tumors because of the problem in determining whether the lesion is primary or secondary, and their relative incidence is difficult to determine. Other malignant tumors have been sporadically reported and these include rhabdomyosarcoma,[36] liposarcoma,[21] angiosarcoma,[39] fibrosarcoma[2,7,21,39] and neurogenic sarcomas.[21,38]

Adenocarcinomas

These tumors arise from the mucosa and form polypoid endoluminal masses, infiltrative annular constrictions or both. Demonstration of tumor within the mucosa is characteristic of primary lesions but may also be seen in advanced metastatic lesions from stomach, colon, ovary or pancreas. Most adenocarcinomas are well differentiated, with mucin producing columnar epithelium forming acinar strictures. Less well differentiated carcinomas occasionally may be difficult to distinguish from anaplastic lymphomas but if mucin can be found using appropriate stains the diagnosis of carcinoma is established. There is sometimes no certain method to distinguish between acinar carcinomas of pancreas and duodenum. Adenocarcinomas are more common in the proximal intestine. Of the 48 tumors, 19 were in duodenum, 16 in jejunum and 13 in ileum. This distribution is similar to that in previous reports (Table 1). Adenocarcinomas tend to metastasize to regional lymph nodes and liver. Peritoneal carcinomatosis also occurs and is more common than widespread metastases to lungs or bones.

Carcinoids

Most intestinal carcinoids are small tumors.[1,2,4,6,7,12,14,17,20,21,30,34,38,39,42,45,47,48,51,53,56] The median diameter was 1.0 cm and the largest tumor was 3.0 cm in diameter. Intestinal carcinoids have a characteristic alveolar nesting pattern. Microacini are common but the ribbon and festoon patterns of hindgut carcinoids are only infrequently encountered. The cells tend to have uniform, round to oval nuclei and granular cytoplasm. In routine processed specimens silver impregnation techniques are unreliable. Small amounts of mucin are frequently seen, and an amyloid stroma is rarely present. Although nuclear pleomorphism is uncommon, even in larger tumors, all carcinoids should be regarded as having malignant potential. Like their counterpart in the bronchus, intestinal carcinoids are often indolent, as indicated by the discovery of approximately a third of them as incidental findings at autopsy. On the other hand, Dockerty reported metastases at the time of diagnosis in 85% of intestinal carcinoids and Vouri found that 33% of patients with carcinoids were dead after 5 years. Ninety-three per cent of symptomatic carcinoids had metastases according to Moertel.[34] The distributions of 38 carcinoids was ileum 25 (66%), duodenum 11 (29%) with only one each in jejunum and Meckel's diverticulum. This differs from other reports, in that of 714 carcinoids with location recorded 84% were in ileum, 5% in the duodenum, 10% in the jejunum, and 1% in Meckel's diverticulum. Symptoms of carcinoid syndrome were present in two of our cases. The syndrome was diagnosed in 16 (2%) of 714 other reported carcinoids. A higher incidence of carcinoid syndrome in patients with intestinal carcinoids has been reported by some authors.[6,49] Carcinoids tend to spread via regional nodes to liver. Disseminated disease beyond the liver is quite uncommon but occasionally ovaries or peritoneal surfaces are involved.

Leiomyosarcomas

Muscular tumors nearly always arise in muscularis propria. The bulk of the tumor may be extrinsic but larger lesions eventually may compress lumen or ulcerate mucosa. Although pleomorphism may be seen with benign tumors, an increased mitotic rate, that is, more than one mitotic figure per high power field (25 fields), establishes the diagnosis of sarcoma.

Of the 11 leiomyosarcomas, 4 were in jejunum and 7 in ileum. Of 421 previously reported cases, 41 (10%) were in duodenum, 156 (37%) in jejunum and 224 (53%) in ileum (Table 1). Locally recurrent tumor with extension into adjacent bowel or other intra-abdominal organs is the typical route of spread. Hepatic metastases are sometimes seen but metastases beyond the abdomen are much less common.

Treatment

Surgical resection is the most common method of therapy for all kinds of tumors. Curative resection was attempted in 44 of 48 adenocarcinomas, all of the carcinoid tumors diagnosed antemortem and all of the leiomyosarcomas. Palliative bypass was performed in the other 4 patients with adenocarcinoma who had liver metastases at the time of operation. Since the route of dissemination of adenocarcinomas and carcinoids is similar, a rational approach to surgical therapy of both is adequate local excision and removal of the regional lymph nodes. The proximity of the nodes draining the intestine to the vascular supply of the jejunum, ileum and proximal colon makes a true radical operation impossible, since this would require sacrifice of nearly all the small intestine and proximal colon. Removal of duodenal carcinomas requires a radical pancreaticoduodenectomy, and right hemicolectomy is usually required when the primary carcinoma is in the distal ileum. Pancreatico-duodenectomy was performed for 5 adenocarcinomas and 2 carcinoids. Right colectomy was included in resection of 4 adenocarcinomas and 5 carcinoids. Wide local resection including mesenteric nodes without sacrifice of the superior mesenteric vessels was the operation for the other adenocarcinomas. Since leiomyosarcomas do not spread primarily via lymphatics, wide local excision was the treatment attempted in all 11 instances. In two cases, right colectomy was also necessary.

Chemotherapy has been almost uniformly unsuccessful. Neither of 2 patients treated with 5-fluorouracil for ileal adenocarcinoma with hepatic metastases survived one year. Poor response of tumors to chemotherapy has been reported previously,[31,44] although some authors[12,42] have found limited response in a few cases. All 3 tumors are radioresistant.

Result

Of 48 patients with adenocarcinomas, 7 were lost to followup. Six (15%) of the remaining were alive after 5 years. Three of these had pancreaticoduodenectomy for duodenal tumors; three had wide excision of jejunal lesions. The 35 other patients died of carcinoma between 4 days and 51 months. Autopsy was done on 25 of these and confirmed recurrence or metastatic tumor. In other reports, the 5-year survival rate for intestinal adenocarcinomas has ranged from 5%[39] to 25%[53].

Patients with carcinoids have the best prognosis. Fourteen of 37 were lost to followup. Seven (30%) of the remaining survived 5 years. Death from disease occurred from 1 to 36 months after diagnosis. Five-year survivals in other reports range from 13% to 62%. Because of the relative indolence of carcinoids compared to adenocarcinomas 5-year survival rates are probably less meaningful, and 10- or 15-year followup data would be a better index of effectiveness of therapy.

Ten of 11 leiomyosarcomas were traced and 2 (20%) were alive and apparently disease-free at 5 years. Recurrent tumor, confirmed by autopsy in 5 instances, was the cause of death between 1 and 48 months in the other 8.

Comment

The relative immunity of the small bowel to development of malignant tumors remains an enigma. Multiple factors may explain the low incidence of malignancy compared to stomach and colon. The fluid alkalinity and rapid transit time of contents may decrease exposure to carcinogens.[27,56] The lower bacterial population and difference in bacterial metabolism possibly results in formation of fewer carcinogenic compounds from bile or other substances than in colon. Protective enzymes such as the benzpyrene hydrolase, which can detoxify potential carcinogens, are present in greater quantities in small bowel than colon,[54,55] and the high concentration of immunoglobulin A may result in greater neutralization of potentially carcinogenic viruses. This idea is supported by the finding of higher incidence of small bowel carcinoma in patients deficient in this immunoglobulin or receiving immunosuppressive therapy. The prevalence (17–20%) of other primary neoplasms in patients with small bowel tumors, also suggests that deficiency in immunologic surveillance against cancer is a particularly important factor in development of these tumors.

The relative rarity of malignancy in small intestine probably decrease suspicion of the possibility of such a lesion when a patient presents with early symptoms. Unfortunately, most malignant tumors of small intestine have spread beyond the site of origin by the time a diagnosis is established, and this circumstance is most responsible for the poor prognosis of these lesions.

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Primary Carcinoma of the Gallbladder

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One-hundred-and-seventeen patients with histologically proven carcinoma of the gallbladder are reviewed. The majority of the patients presented with advanced disease with extension and metastasis to the liver and to lymph nodes along the common bile duct. Four patients had localized disease recognized at the time of operation; two were treated with cholecystectomy and two with cholecystectomy and hepatic resection. There were no five-year survivals among these patients. Fourteen patients had clinically inapparent carcinoma at the time of cholecystectomy; the diagnosis being established postoperatively by histologic examination of the excised gallbladder. There were two five-year survivors in this group of patients. Both survivors had early papillary carcinoma confined to the gallbladder wall. The remaining patients with inapparent carcinoma died within three years of the time of operation with recurrent carcinoma. The present report and review of the recent literature emphasizes the poor prognosis associated with carcinoma of the gallbladder. Even with apparently localized lesions, the survival rate is extremely poor. Extended resection, while not of proven value, may improve the survival rate.

GALLBLADDER CANCER in biliary tract operations has been encountered in up to 4% of cases, with most series indicating the incidence to be about 1%.[3] Glenn[9] has stated that in patients over 65 years operated upon for cholelithiasis, 10% would be found to harbor a carcinoma of the gallbladder. The disease, while uncommon, is not rare and the poor prognosis of this tumor is widely recognized.[2]

Most patients coming to operation for suspected carcinoma of the gallbladder have advanced disease. Discovery of patients with early disease usually is fortuitous, the diagnosis of carcinoma being established only postoperatively, after histologic examination of a gallbladder excised for treatment of symptomatic cholecystitis. The further management and prognosis of patients in this clinical situation is not well established.

This report summarizes the course of patients with carcinoma of the gallbladder seen at the University of Iowa Hospitals from 1938 to 1970. It was our purpose to review the clinical features of carcinoma of the gallbladder with particular attention to the results of treatment of very early lesions by cholecystectomy.

Clinical Material

The clinical records of 117 histologically proven cases of primary carcinoma of the gallbladder were reviewed. The diagnosis had been established at operation in 103 patients; 14 were diagnosed at post mortem examination.

For the purposes of this report, the patients have been divided into four groups:

Group A (localized inapparent disease): 14 patients in whom a diagnosis of carcinoma of the gallbladder was not suspected clinically and was not made intraoperatively; cholecystectomy with or without common bile duct exploration was performed and the presence of cancer discovered later during histologic examination of the operative specimen.

Group B (localized potentially curable disease): four patients in whom the malignant nature of a localized gallbladder cancer was recognized at operation and in whom a potentially curative procedure was possible.

Group C (palliative therapy): 28 patients in whom palliative operative procedures were performed after initial exploration demonstrated disseminated carcinoma.

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Group D (late disease): 71 patients in whom advanced disease was found at operation or autopsy and in whom no attempt was made at palliative or definitive therapy.

The mean age of all patients was 67 years; there were 89 women and 28 men (3:1). Pain was the most frequent complaint. Jaundice and a palpable mass each were seen in more than half the patients with advanced disease and usually were present together. There were no unique clinical features of gallbladder cancer early or late in the course of the disease.

There were no diagnostic laboratory abnormalities. Serum bilirubin and alkaline phosphatase were elevated in patients with obstructive jaundice. Many patients with advanced disease had anemia, hypoalbuminemia and abnormal liver function tests. Oral cholecystograms were performed in most patients who were not jaundiced; in no case was the gallbladder visualized. Upper gastrointestinal series were performed in 77 cases; abnormalities were identified in a third of these examinations. The most common abnormality, seen in 21 patients in groups C and D, was external compression of the lateral border of the duodenum. In five patients there was a roentgenographic picture of gastric outlet obstruction which subsequently proved at operation to be due to invasion of the duodenum by tumor.

The most frequent preoperative diagnoses were cholelithiasis in early cases and pancreatic carcinoma in more advanced cases. A correct preoperative diagnosis was made in only 11 instances, a diagnostic accuracy of less than ten per cent.

The operative procedures are listed in Table 1. There were 119 operations performed in 103 patients. The operative mortality (30 days) for all procedures was 18%. Most of the patients who died postoperatively were in an advanced stage of disease (Group D) at the time of exploratory laparotomy. There were no operative deaths in Group A patients.

TABLE 1. *Operations Performed in Patients with Gallbladder Cancer*

Laparotomy and Biopsy		62
Cholecystectomy: alone	19	
with common duct exploration	7	
with right hepatic lobectomy	1	
with excision of hepatic bed	1	
Total		23
Cholecystostomy		3
Cholecystojejunostomy		3
Choledochoduodenostomy		1
Excision of biliary-enteric fistula		2
Gastroenterostomy		7
Drainage of abscess		3
Hepatic artery cannulation		3
Other procedures		7

TABLE 2. *Extent of Spread of Carcinoma at the Time of Diagnosis*

	Group B	Group C	Group D	Total
Total Patients	4	28	71	103
Liver	1	27	70	98
Common Duct Lymph Nodes	1	19	64	84
Omentum & Peritoneum	0	10	19	29
Duodenum and Stomach	0	4	10	14
Colon	0	1	11	12
Pleura & Lung	0	0	7	7
Other*	0	0	6	6

Excluding Group A, 89 patients were diagnosed at operation and 14 at postmortem examination.

* Includes intracranial metastasis (3 patients) and adrenal metastasis (5 patients).

Cholecystectomy was performed in 28 cases; in 14 patients, it was done without intraoperative recognition of the presence of carcinoma (Group A). A small group of four patients, in whom carcinoma grossly was localized to the gallbladder and was correctly diagnosed intraoperatively, had cholecystectomy as part of definitive excisional therapy for their tumor (Group B). In two of these patients no further procedures were carried out; one other patient had a right hepatic lobectomy and another had a wedge resection of the hepatic bed of the gallbladder in addition to cholecystectomy. The one postoperative death in Group B occurred in the patient in whom hepatic lobectomy had been performed. In ten further patients, cholecystectomy was carried out as a part of the operative palliation of disseminated carcinoma.

The majority of tumors were adenocarcinoma (98 of 117); of these, only three were papillary in type. There were seven epidermoid carcinomas and 12 tumors were classified as undifferentiated. The most frequent site of invasion or metastasis was to the right lobe of the liver (98 of 117) and to lymph nodes along the common bile duct (84 of 117). Many patients also had hepatic metastases at a distance from the gallbladder bed or tumor implants in the peritoneum or omentum. Direct invasion of the duodenum by tumor was found in 14 patients, the hepatic flexure of the colon was involved in 12 cases. The extent of invasion or metastasis at the time of diagnosis is summarized in Table 2.

Survival

The five-year survival rate for all patients was 1.7%. Three-fourths of the patients who had their diagnosis established preoperatively or intraoperatively had succumbed to their disease within six months. The mean survival of the four patient groups is summarized in Table 3.

The course of patients in whom the diagnosis of carcinoma was not apparent to the surgeon at the time of

TABLE 3. *Mean Survival from Time of Diagnosis (Operation) in Patients with Gallbladder Cancer*

Group A	Inapparent Disease	16.7 months*
Group B	Localized Disease	24.7 months†
Group C	Palliative Therapy	15.4 weeks
Group D	No Operative Treatment Possible	8.5 weeks

* Excludes patient dying 21 years later of unrelated cause.
† Excludes postoperative death.

operation and was established by histologic examination of the excised gallbladder is summarized in Table 4. Two of the 14 patients in this group survived more than five years; a group survival rate of 14.3%. Both survivors had papillary adenocarcinoma. In one, the tumor involved only the mucosa of the gallbladder; in the other, there was evidence of perineural spread but no involvement of the gallbladder serosa. Of the 12 Group A patients who did not survive five years, three had carcinoma confined to the gallbladder wall without serosal involvement. Recurrent gallbladder carcinoma was the cause of death in 11 of the 12 nonsurviving Group A patients. The other patient returned to the hospital 11 months after cholecystectomy with superior mesenteric artery occlusion. At laparotomy, in addition to advanced necrosis of small bowel, two small tumor implants were noted in the gallbladder bed; the patient died two days later of sepsis. Post mortem examination demonstrated additional small metastatic implants in the left liver lobe and in a splenic pedicle lymph node.

Discussion

The association of gallbladder carcinoma and cholelithiasis is well established. In his collective review, Arminski[3] found gallstones present in 73% of patients with gallbladder cancer; similar figures of stone incidence are noted in the later reviews of Strauch,[26] Litwin[17] and Hart and colleagues.[14] Gallstones were definitely present in 69% of our patients; in only four was there definite mention that stones were absent.

TABLE 4. *Clinical Features of Patients with Inapparent Carcinoma of Gallbladder (Group A)*

Age	Sex	Histologic Diagnosis	Survival (months)
83	F	Adenocarcinoma	7.5
66	F	Adenocarcinoma	14
83	F	Adenocarcinoma	9
81	M	Adenocarcinoma	23
57	F	Adenocarcinoma	4
70	F	Epidermoid carcinoma	13
83*	F	Adenocarcinoma	11
67	F	Adenocarcinoma	14
59	F	Papillary Adenocarcinoma	35
61	F	Adenocarcinoma	18
65†	F	Adenocarcinoma	34
47†	F	Undifferentiated carcinoma	10
72	F	Papillary Adenocarcinoma	alive 6 yr.
60	F	Papillary Adenocarcinoma	died 21 yr.‡

* Died of unrelated cause 11 months postop but had recurrent and metastatic carcinoma (see text).
† Received chemotherapy after recurrence of carcinoma.
‡ Death due to unrelated cause.

The etiologic relationship between gallstones and gallbladder carcinoma is unclear. Wenkert and Robertson[30] followed 781 patients with "silent gallstones" and noted that over an 11-year period only 0.4% developed carcinoma. Similarly, Lund[18] found that of 526 patients being followed with nonoperative management of asymptomatic cholelithiasis, only 1% developed a carcinoma of the gallbladder; but, most clinical reports of gallbladder cancer take pains to point out the frequent association of gallstones and gallbladder carcinoma.

The clinical features of carcinoma of the gallbladder are indistinguishable from those of cholecystitis and cholelithiasis. In the later stages of gallbladder cancer, the clinical picture is most frequently one of metastatic liver disease and obstructive jaundice. Most patients who present with early lesions have symptoms because of cholecystitis rather than their tumor. Seven of the 14 patients in our Group A (inapparent disease) presented with acute or subacute cholecystitis. The difficulty of diagnosing cancer under these circumstances is apparent.

Among our patients, 45% gave a history of symptoms of cholecystitis which had existed for more than one year prior to operation. Of those patients who were considered potentially resectable for cure (Groups A and B), 61% had a history of longstanding biliary tract symptoms. Three patients, all with advanced disease, had had a cholecystostomy up to 23 years previously as treatment of complicated cholelithiasis. The high frequency of longstanding symptoms attributable to the biliary tract in patients with gallbladder carcinoma has been noted by others.[2,3,12,16,23]

Preoperative roentgenographic studies were of little value in establishing a diagnosis of gallbladder carcinoma. Hardy and Volk[12] have described a patient in whom a subsequently proven carcinoma presented as an intramural filling defect in a visualizing oral cholecystogram. Mooring[21] has described a variant of cystic duct obstruction seen on intravenous cholangiography which he believes is diagnostic of carcinoma of the gallbladder. Although other authors[1,11] have reported the presence of gallbladder cancer in patients with normal oral cholecystograms, there were no such instances among our patients.

It is of interest that a third of our patients in whom an upper gastrointestinal series was performed showed abnormalities, the most common of which was compression of the lateral part of the duodenum. Invasion of the duodenum by tumor was documented in 14 cases and, as previously mentioned, five of these patients had a clinical and roentgenologic picture of gastric outlet obstruction. Tanga and Ewing[27] have reported three patients with carcinoma of the gallbladder presenting as gastric outlet obstruction. Khilnani[15] has described compression of the first portion of the duodenum with loss of mucosal folds as a characteristic finding in duodenal involvement by gallbladder carcinoma. These x-ray findings occur with advanced disease and are of little help in early diagnosis of potentially curable cancers.

The most frequent sites of spread of gallbladder cancer are to the adjacent liver and to lymph nodes along the cystic and common bile ducts. In our patients, metastases to the gallbladder bed were present in 84 per cent and to lymph nodes along the common bile duct in 72%. Fahim and colleagues[6] elaborated on the mode of spread of carcinoma of the gallbladder; nodes along the common bile duct were involved in 20% of early cases which potentially were curable. Because of this finding, they recommended that operations for cure should include wedge resection of the hepatic gallbladder bed combined with en-bloc excision of lymph nodes along the common bile duct to the upper border of the duodenum. More extended resection in patients in whom the disease is grossly apparent does not increase the survival rate.[3,16,22]

Both of our long term survivors had a well differentiated papillary adenocarcinoma. Similarly, the only five-year survivor reported by Frank and Spjut[7] had a papillary adenocarcinoma as did two of the long term survivors reported by Fahim and colleagues.[5] Hart and Modan[13] have emphasized the better prognosis of papillary adenocarcinoma of the gallbladder. However, Glenn and Hayes[10] have found no influence of histologic tumor type on survival rates. In the experience of some authors,[10,18] papillary lesions are frequently anaplastic at their base.

Discovery of patients at an early stage of gallbladder cancer is fortuitous and not common. Only 17% of our patients were considered potentially curable. A similar low incidence of early lesions has been reported by others.[12,20,27,28] In many series, the only survivors are those in whom the carcinoma is not apparent at the time of operation. Both of the five-year survivors among our patients were diagnosed only by histologic examination of the excised gallbladder. Table 5 summarizes survival rates in patients with early carcinoma of the gallbladder treated by cholecystectomy. Even with early lesions, survival after cholecystectomy has been disappointing.

TABLE 5. *Results of Cholecystectomy in Treatment of Localized Gallbladder Carcinoma*

Author	Total Cases	Localized Cases	No. of 5 Year Survivors
Chandler and Fletcher[4]	66	10	2
Fahim *et al.*[5]	151	25	8*
Frank and Spjut[7]	16	16	1
Gerst[8]	132	22	7
Gradisar and Kelly[11]	41	5	1
Marcial-Rogas and Medina[19]	28	14	1
Ram[23]	47	10	0
Salwan[24]	96	15	2
Strauch[26]	70	10	3
Thorbjarnarson and Glenn[29]	90	23	3
Present Report	117	16	2
Totals	838	166	30

* Two of these patients developed recurrence more than 5 years postoperatively.

What can be done to improve the survival of patients having carcinoma of the gallbladder? Obviously, once dissemination from the gallbladder has occurred, even extensive resectional therapy will not improve survival. However, in those lesions which are still confined to the gallbladder and its immediate environs, extended resectional therapy should improve end results. The difficulty is in making the diagnosis when the lesion is still so confined.

Patients over 65 years have an appreciable risk of harboring a gallbladder carcinoma. If every gallbladder removed in older patients were examined by the surgeon in the operating room prior to completion of the operation, surely some "inapparent" carcinomas would be noted and extended resection of the gallbladder bed and common duct nodes could be carried out immediately. Although extended resection has done little to improve overall survival rates,[10,22] there has been an inadequate clinical trial in patients with localized carcinomas.

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Five to Twenty Year Followup after Surgery for Chronic Pancreatitis in 148 Patients

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One-hundred and forty eight patients operated upon for chronic pancreatitis were reviewed retrospectively in 5–20 year followup. Treatment was by drainage of the duct of Wirsung to adefunctionalized jejunal loop, distal pancreatectomy, pancreato-duodenectomy, splanchnicectomy with an operative mortality of 5%. Influence of clinical and anatomical data upon long term survival and symptomatic results was studied. Among Wirsungo-jejunostomy, distal or cephalic pancreatic resections, survival rates were highest with drainage of the duct of Wirsung and lowest with the pancreato-duodenectomy. Retrospectively, post-operative alcoholism appeared as the alone factor affecting long-term survival. Pancreatic insufficiency and liver cirrhosis were main causes of death. Among the survivors, the percentage of good symptomatic results ranged from ⅓ with splanchnicectomy to 6 of 8 after duodeno-pancreatic resection. Alcohol abstinence affected sypmptomatic results but at a lesser degree than for survival. It was observed that when left pancreatectomy was performed, drainage of the remaining duct of Wirsung into the jejunum significantly improved the good results from 40% to 75%. In the group of wirsungo-jejunostomies without pancreatic resection, it was found that pancreatic calcifications and a large diameter of the duct of Wirsung at the time of operation were favorable prognostic factors.

A VARIETY OF SURGICAL PROCEDURES has been advocated in the treatment of chronic pancreatitis. The conflicting reports regarding their effectiveness justifies a comparative study of different operations performed by a single group of surgeons within a similar population over a concurrent period of time. Since spontaneous and temporary regression of symptoms is not unusual in this condition, a minimum followup period is essential for a proper evaluation of the postoperative result.

This report consists of a five to twenty year comparative followup study in a total of 148 patients with chronic pancreatitis each of whom had either a distal pancreatectomy, pancreatico-duodenal resection, pancreatico-jejunostomy without resection, or splanchnicectomy.

Material and Methods

All the patients in this study were suffering from primary or idiopathic pancreatitis. All cases of pancreatitis related to ulcer or biliary lithiasis were eliminated.

A total of 148 patients with severe chronic pancreatitis were operated on by the authors prior to December 31, 1966. There were 135 male (90%) and 13 female. The majority of these patients (133) suffered from primary chronic pancreatitis. In this group the role of alcoholism was important since 91 (61%) were considered alcoholics. One hundred and three (68%) had radiologic or histologic evidence of pancreatic calcifications (Table 1).

Two patients had familial pancreatitis and two others chronic pancreatitis secondary to trauma. In 11 patients chronic pancreatitis appeared one to two years after an initial attack of acute idiopathic pancreatitis.

One hundred forty four of the 148 patients had pain as their chief complaint with an average history of 4.4 years. Weight loss occurred in 135 cases with a mean loss of 8.9 kg. An abnormal glucose tolerance was found in 52, steatorrhea in 47, jaundice in 45, clinical diabetes in 19, and portal hypertension with gastrointestinal hemorrhage in 10. Gross or radiologic evidence of pseudocyst was present in 29 patients (Table 2).

There were but four patients who were operated on for symptoms other than pain, 2 for hemorrhage, one for ascites, and one for jaundice.

In this group of 148 patients 71 were subjected to a left pancreatectomy (39 with an associated pancreatico-jejunostomy), 45 had a Wirsungo-jejunostomy done, 16 underwent pancreatico-duodenectomy, and 16 had a splanchnicectomy.

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TABLE 1. *General Features of Operated Fatients*

	Cases	Sex	Mean Age	Mean Duration	Pancreatic Calcif.	Alcoholics	Histologic	Impairment
Total Group	148	M = 135	39.8 (15–63)	4.4 (0.5–15)	103	91	Moderate	26%
							Severe	74%
Distal Pancreatectomy	71	63	39.4 (21–63)	4.4 (0.5–15)	43	39	Moderate	37%
							Severe	63%
Duodeno-pancreatectomy	16	15	39.1 (30–58)	4.9 (1–11)	15	11	Moderate	19%
							Severe	81%
Wirsungo-jejunostomy	45	41	40.8 (15–63)	3.9 (0.5–15)	36	32	Moderate	25%
							Severe	75%
Splanchnicectomy	16	16	40.6 (31–60)	3.8 (1–10)	9	9	Moderate	44%
							Severe	56%

Eight patients died during the first two postoperative months resulting in an overall operative mortality of 5.5%.

The postoperative condition of the 140 surviving patients was evaluated either after rehospitalization or by direct inquiry of the patients and their physicians. Thirty-five of them have required reoperation (25%) with three postoperative deaths (9%).

Twenty patients died from six months to five years after surgery leaving 120 that have been followed for more than five years. Forty eight of these have been followed more than 10 years. Results were evaluated on the basis of four criteria: absence of pain and diarrhea, weight gain, and return to work. The findings were classified as good, fair, and poor as outlined in Table 3.

An attempt was made to correlate pre- and per-operative findings, age, duration of symptoms, pancreatic calcification, alcohol consumption, ductal dilatation, and histological changes with survival and quality of operative results.

Results

I. Distal Pancreatectomy

A total of 71 left pancreatectomies (Fig. 1) were performed. A complementary pancreatico-jejunostomy (Fig. 2) was performed in 39 (51%) who exhibited a dilated Wirsung's duct or an intra-pancreatic pseudocyst of the head of the pancreas by per-operative pancreatography.

TABLE 2. *Symptoms in 148 Patients with Chronic Relapsing Pancreatitis*

Pain		144	
Loss of weight		135 (m: 8.9 kgs)	
Steatorrhea		47	
Jaundice		45	
Gastrointestinal Hemorrhage with Sectiorial P. Hypertension		10	
Pancreatic ascites		5	
Diabetes		19	71
Glucose Intolerance		52	
Pancreatic Pseudocysts	Extra P.	9*	
	Intra P.	20	

* 2 right and 7 left extra-pancreatic pseudocysts treated by P. Resection.

Of this group 88% were males with a mean age of 39.4 years (21–63 years), mean duration of symptoms 4.4 years (0.5–15 years), and 60% exhibited pancreatic calcification.

A. Mortality. Five patients died within the first two postoperative months (6%).

2 with pancreatic fistula and subphrenic abscess.
1 with gastrointestinal bleeding.
1 with colic fistula and cachexia.
1 with a cerebral hemorrhage.

Ten patients died from six months to five years postoperatively.

4 with pancreatic insufficiency and cachexia.
2 with alcoholic cirrhosis and coma.
2 with cerebral hemorrhage.
1 with acute pancreatic necrosis.
1 with sudden unexplained death.

Eighteen patients died from six to twelve years postoperatively.

8 with alcoholic cirrhosis and coma.
6 with pancreatic insufficiency.
2 with acute pancreatic necrosis.
1 unknown.
1 sudden unexplained death.

It is important to note that in this group of patients left pancreatectomy was associated with an overall mortality rate of 46%. Thirteen patients died of further progression of their pancreatitis with cachexia, pain, diabetes, or acute pancreatic necrosis. However, ten patients who continued to drink heavily died of cirrhosis after com-

TABLE 3. *Quality of Operative Results*

	Pain	Diarrhea	Gain of Weight	Activity
Good results	None	None	>5 kg	Normal
Fair results	Rare	Rare	<5 kg	Normal
Bad results	No Relief or Slight Improvement	Rare . . . . . . or Permanent	0 or Loss	Reduced or None

plete or nearly complete relief of their pancreatic symptoms, particularly pain. This latter finding emphasizes the effect of alcoholism on the long-term results of surgical efforts.

In the group of 28 patients that died from six months to twelve years, the functional results of operation were: good 43%, fair 7%, and poor 50%.

On the other hand, in the group of 38 long-term survivors (5 to 20 years) we found good results in 68%, fair in 11%, and bad in 21%.

The only significant factor in prognosis was persistence of alcoholic addiction: 82% alcoholics among patients who succumbed versus 35% among survivors ($p = 0.001$).

Age, disease duration, calcification, histological changes, had no correlation with morbidity or mortality.

B. Functional Results. In the 56 patients who survived over five years, 62% had good results, 10% fair, and 28% bad. Two factors appeared significant: 1. Pancreaticojejunostomy improved significantly the operative results. Thirty-two patients with this complementary procedure exhibited 75% good results versus 40% good results in those without such drainage ($p < 0.01$). 2. Pancreatic calcification was a favorable finding. There were 74% good results in 34 patients with calcification and 42% good results in 22 cases without calcification ($p < 0.05$).

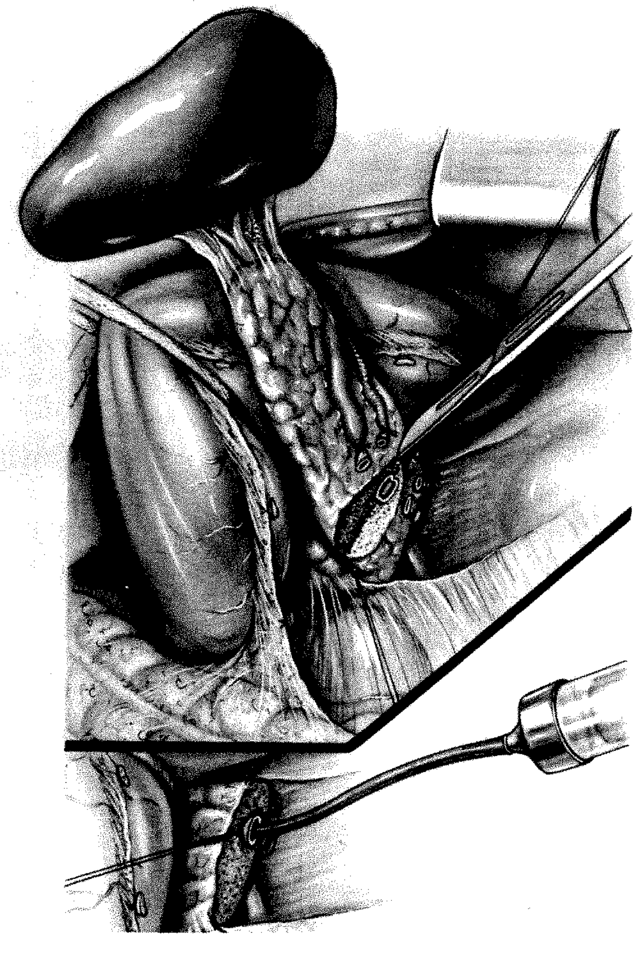

FIG. 1. Left pancreatectomy. Division of the pancreatic isthmus after preliminary ligation of the splenic vessels. Note the dilated duct of Wirsung. Pancreatography is performed to ascertain patency of the residual ductal system.

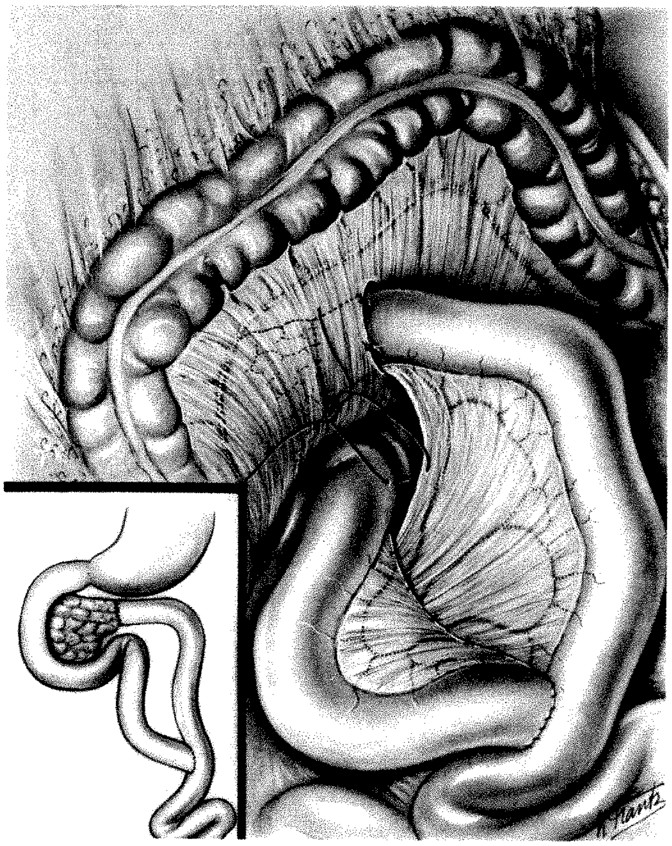

FIG. 2. Complementary pancreatico- or Wirsungo-jejunostomy. Performed with a dilated duct or in the presence of ductal pathology demonstrated by pancreatography. A Roux-Y limb of proximal jejunum is passed through the transverse mesocolon for the anastomosis.

Since patients with calcifications usually have a dilated duct system the population of these two groups is almost identical.

Persistence or cessation of alcoholic intake did not play the same significant role in functional results as it did in mortality in this group. In 29 operated patients who became temperate there were 68% good results and 17% bad results. Among 24 who continued drinking there were 50% good results and 42% bad ($p > 0.05$).

C. Reoperations. Fourteen (21%) were reoperated from six months to fourteen years after left pancreatectomy. Three had a splanchnicectomy without control of the pancreas; two failed to show any improvement.

In the remaining eleven who were laparotomized, six had a patent anastomosis but progression of their pancreatic disease; 2 were treated by transperitoneal splanchnicectomy without any success; four underwent a choledochoduodenostomy with one death, one good and two bad results.

The remaining five were reresected with a new pancreatojejunostomy; this resulted in two good and three poor results.

II. Pancreatico-Duodenectomy (16 patients—Figs. 3 and 4)

The general features of this group are summarized in Table 2. The outstanding feature in these patients was the high incidence of pancreatic calcification (93%).

One patient died three weeks after operation of recurrent intestinal obstruction.

Eight patients died six months to six years after operation. This high (50%) late mortality can be attributed to postoperative metabolic disturbances: pancreatic insufficiency and malnutrition (2 cases), cirrhosis (2 cases), hypoglycemic coma (2 cases), unexplained death (2 cases).

Eight patients survived more than five years, six with a good result, one fair, and one poor result. There were no re-operations in this group.

III. Pancreato-Jejunostomy (45 Cases—Fig. 5)

A. Mortality. Two patients died during the two first postoperative months (4%). One with a pancreatic fistula and septicemia. The other in diabetic coma. Three died from six months to three years after operation. Two with pancreatic insufficiency and one with alcoholic cirrhosis. Twelve died from between five and ten years after operation from pancreatic insufficiency (4), cancer (1), cirrhosis (3), intercurrent disease (3), unexplained (1).

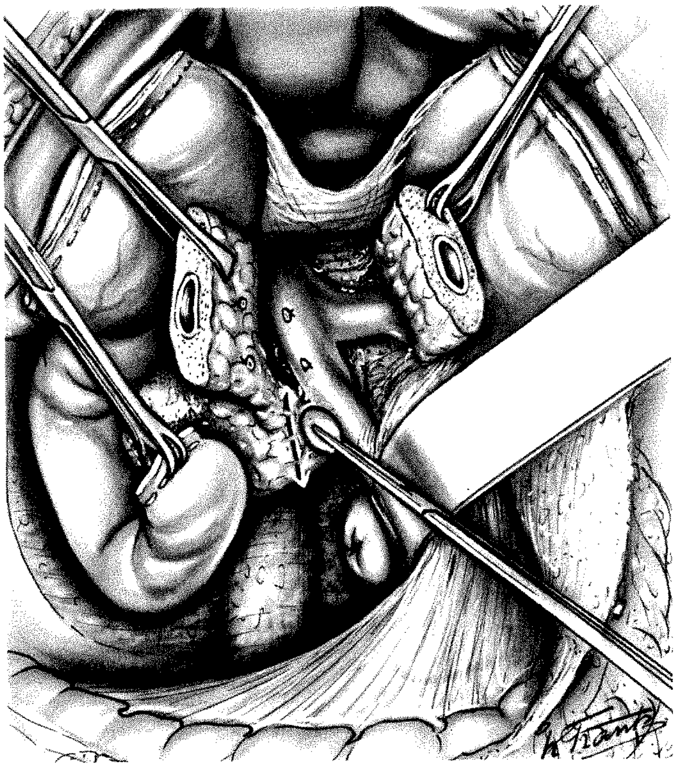

FIG. 3. Pancreaticoduodenectomy-Exeresis. The head of the pancreas is shown being carefully dissected from the superior mesenteric vein. The small section of the uncinate process shown by the dotted lines may be left in place.

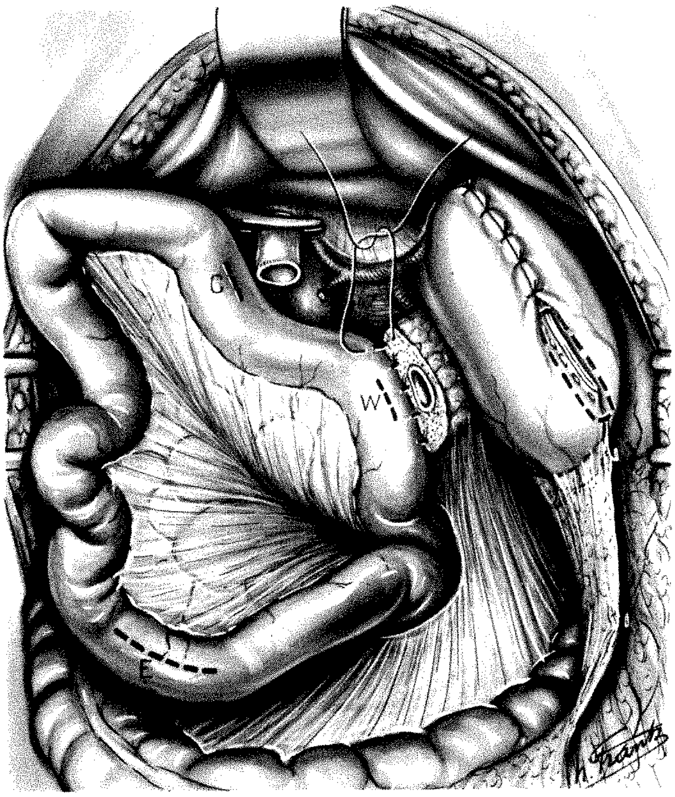

FIG. 4. Pancreaticoduodenectomy-Reconstruction. The pancreatic capsule and duct of Wirsung are anastomosed separately in an end to side fashion. At the apex of the jejunal loop an end to side choledocho-jejunostomy is performed. The gastrojejunostomy is placed approximately 30 cm from the apex.

The overall late mortality was 36%, the main course of death being progression of pancreatic disease in seven of these patients.

A comparison of the fifteen late deaths and the 28 survivors in this group revealed little difference in the effectiveness of the surgery. In the group of patients who succumbed there were 40% bad results.

Alcoholism on the other hand played a significant role since of those who fell into the late mortality group, 79% continued to drink, whereas only 43% continued to imbibe in the long-term survivors ($p = 0.01$).

B. Factors Influencing Long-Term Results. There were forty patients who survived more than five years and 48% of these had a good result, 15% fair, and 37% poor. In this group two factors played an important role, alcoholism, and the size of the Wirsung's duct.

The twenty-one patients who broke off drinking postoperatively demonstrated 66% good results while the 16 patients who continued had but 25% good results ($p < 0.01$).

In 19 patients who had a Wirsung's duct measuring greater than 10 mm. in diameter there were 72% good results whereas in 10 patients with a duct smaller than 5 mm. there were but 39% good results ($p = 0.01$).

C. Reoperations. Eighteen patients in this group or 40% required re-operation from five months to five years after pancreato-jejunostomy. In three a left splanchnicectomy provided relief. Nine patients were found to have a stenosis of the pancreato-jejunostomy. In six of these the anastomosis had been performed with a duct less than 5 mm in diameter. A new anastomosis was re-established and in two a complementary splanchnicectomy was performed. There were four good and five bad results.

Three patients with recurrent pain were found to have patent anastomoses. Two were splanchnicectomized and one had a left pancreatectomy. There was one fair and two bad results.

Two choledochal and one duodenal stenoses were treated by choledochoduodenostomy and gastrojejunostomy respectively with one death, one good, and one poor result.

IV. Splanchnicectomies

Sixteen patients had a transperitoneal splanchnicectomy performed as a primary procedure (Table 2). Ten of these were left sided, five right sided and one bilateral. In addition, pancreatic biopsy and pancreatography was performed in every patient.

General features of these patients were similar to the others except for a lower incidence of calcification (56%).

A five to twelve years followup of this group revealed five good, two fair and nine bad results. These patients were reoperated; two had left pancreatectomy with one fair and one bad result; one underwent a pancreato-jejunostomy without success.

Thirteen additional splanchnicectomies were performed as secondary or complementary procedures at the time of reoperation as detailed in the previous groups. Overall results in this group was three good, one fair, and nine bad.

Considering both groups together splanchnicectomy as a single or supplementary procedure yielded a good result in one out of three operations.

Discussion

Careful studies of large groups of medically treated patients (1–10) have demonstrated a cyclical fluctuation in the evolution of clinical pancreatitis. Approximately one-third of patients are found free of symptoms during periods ranging from months to one or two years. This fact must be kept in mind in evaluating operative results. Therefore, an adequate minimum followup period (two years in this study) is necessary before classifying a "good result".

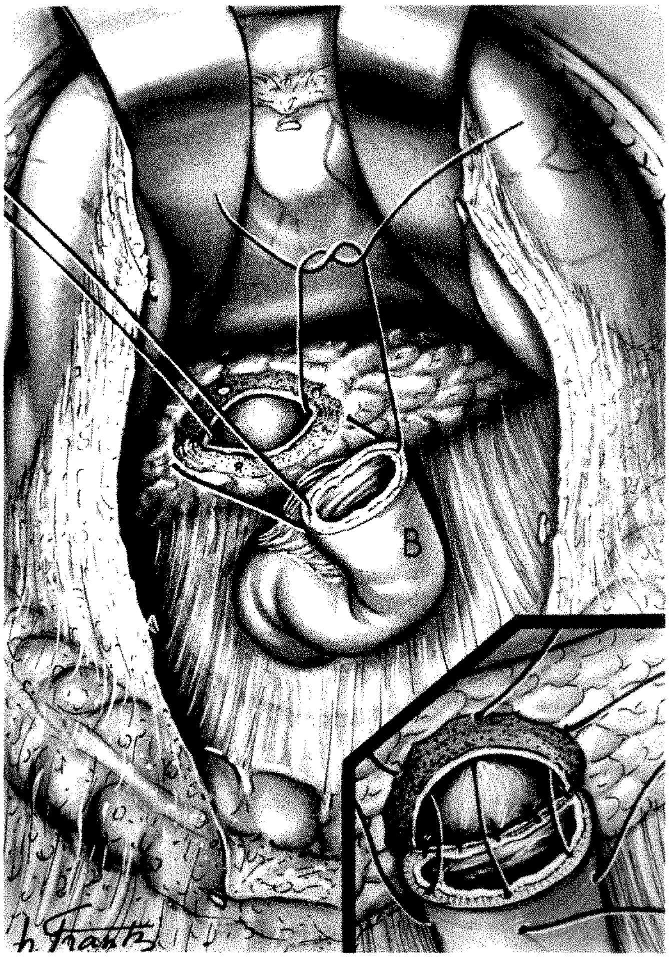

FIG. 5. Pancreato-jejunostomy. A Roux-Y limb of proximal jejunum is passed through the transverse mesocolon and anastomosed to the dilated Wirsung's duct with interrupted non-absorbable sutures.

Analysis of our surgical results reveals a clear superiority for resection (duodeno-pancreatectomy and left pancreatectomy with drainage) which provided 75% good results as compared to Wirsungo-jejunostomy and splanchnicectomy with 49% and 33% good results respectively.

Others have reported a range of results similar to ours. 68–73% good after duodenopancreatectomy (5–15), 70–78% after distal pancreatectomy (12–15), and 44–60% after Wirsungo-digestive anastomoses (11–15).

The results of splanchnicectomy, on the other hand, are conflicting. White and Mallet Guy[16] reported 69% satisfactory results in 46 patients with fibrous or calcifying pancreatitis while others such as Warren[15] have abandoned the procedure.

In our series the age of the patients, duration of disease, and severity of the histologic changes did not influence the operative results.

Priestley and ReMine[13] on the other hand found a better result in a small series if histologic changes were not severe.

The prognostic importance of alcoholism has been emphasized by Warren,[15] Priestley,[13] and Guillemin.[5] Contrary to our expectations, this factor was not statistically significant in our symptomatic results. Some patients who were unable to stop drinking continued pain free over many years before they eventually died of alcoholic cirrhosis.

The excellent statistical correlation between functional results and the size of Wirsung's duct or existence of calcification emphasizes the paramount importance of these anatomic factors. When Wirsungo-jejunostomy, with or without left pancreatectomy, was performed with a grossly dilated Wirsung's duct we were able to provide 70–75% good results, similar to the results with duodenopancreatectomy.

In most patients, bad results appeared at reoperation to be due to unrecognized pancreatic obstruction or retention. Careful Wirsungography and performance of meticulous large anastomoses are basic elements in the surgery of pancreatitis. Nevertheless, after distal pancreatectomy and drainage, we were left with 38% overall failure in patients with a patent anastomosis and no sign of pancreatic retention.

The cause of these latter failures remains unexplained. Ganglionectomy was always unsuccessful in these patients. Pancreaticoduodenectomy, subtotal, or total pancreatectomy might yield better results in non-alcoholic patients but like Duval[5] we have been impressed by the hazards and high failure rate of these radical reoperations.

Analysis of a cumulative survival curve (Fig. 6) shows that the superiority of resectional procedures as to functional results is vitiated by a significant late mortality. Pancreatic insufficiency complicated by malnutrition, pulmonary sepsis or tuberculosis, diabetic or hypo-glycemic coma, and acute pancreatic necrosis are liable for 42% of late deaths. Many other patients who continue to drink heavily die with alcoholic cirrhosis which accounts for 33% of this long-term mortality. Routine liver biopsy in the course of these operations reveals frequent and hepatic changes of fatty and periportal inflammatory infiltrates. After pancreatectomy these lesions progress to an extensive sclerosis. Like gastrectomy, pancreatectomy seems to induce evolution to hepatic cirrhosis.

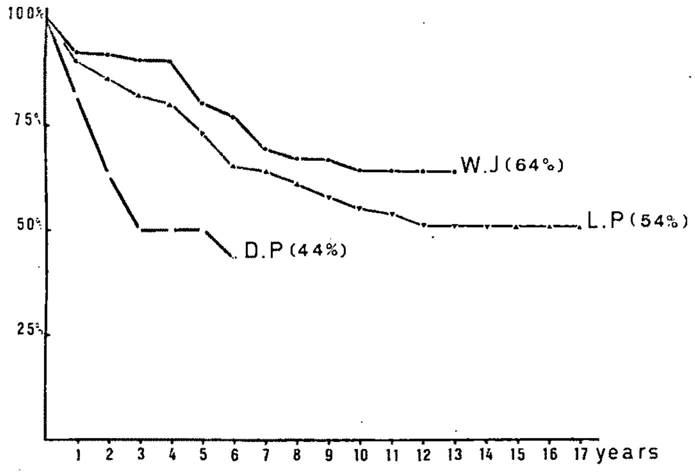

FIG. 6. Cumulative Survival. It is apparent that the superior functional results of duodenopancreatectomy (DP) are vitiated by a high mortality. Survival is greatest after drainage without resection (W.J.) Left pancreatectomy (LP) reveals a greater incidence of early deaths.

After pancreatic drainage without resection mortality is lower (36%) and the frequency of complicating cirrhosis is reduced. Again we must keep in mind that a 30% mortality has been reported in a group of severe but non-operated patients with chronic pancreatitis.[14]

Figure 6 also reveals that the chronology of death is also different when pancreatic resection and drainage procedures are compared. After resection early deaths in the first three or four years postoperatively are much more frequent than after pancreatic drainage. The particular frequency of cirrhosis in these early deaths permits speculation that progression of hepatic lesions could be particularly rapid after gastro-duodenectomy and cephalic pancreatectomy.

In the selection of operative procedures we must distinguish between temperate patients or those who are able to stop drinking, and the alcoholics who cannot.

In the temperate group resection would seem indicated if the local lesions are severe. Distal resection can be utilized if lesions are localized or predominant in the left side of the gland or if angiography demonstrates a sectorial portal hypertension.[7] A pancreatojejunostomy must also be provided if there is any evidence of ductal obstruction or dilatation by Wirsungography.

More often, pancreatic lesions will predominate in the right half of the pancreas. Cephalic calcification, duodenal or choledochal stenosis, poor uptake on Seleno-Methionine Scan[8] must lead to pancreatico-duodenectomy.

When diffuse pancreatic calcification is found we are reluctant to perform subtotal pancreatectomy.[3] This procedure has not been covered in this study because we have used it for less than five years. However during this brief period of time our experience has been less than gratifying because of recurrence of pain or secondary choledochal stenosis. Therefore in non or reformed alcoholics with severe, generalized lesions we prefer duodenopancreatectomy with a large pancreato-jejunostomy which is less subject to secondary deterioration and postoperative diabetes.

In alcoholic patients pancreatic resection must be avoided. A large side to side Wirsungo-jejunostomy is to be preferred if Wirsung's duct is dilated. In this type of patient we defer operation as long as possible awaiting pancreatic calcification and dilatation of Wirsung's duct.

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A Comparative Study of the Effects of Carbon Dioxide and Perfusion Rewarming on Limited Circulatory Occlusion During Surface Hypothermia, Under Halothane and Ether Anesthesia

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Effects of the use of 5% CO_2 and surface-rewarming or perfusion-rewarming on safe total circulatory occlusion time, blood gases and carbohydrate metabolism were studied in 25 dogs subjected to surface hypothermia (18 C) and 30 minutes of circulatory occlusion under halothane or ether anesthesia. Under halothane anesthesia, all animals with 100% O_2 developed motor disorders while one of five surface-rewarmed dogs and none of the perfusion-rewarmed dogs developed motor disorders with 5% CO_2. Under ether anesthesia, all were normal with either 100% O_2 or when 5% CO_2 was added. Ventricular fibrillation occurred in one dog at 21C under halothane anesthesia with 5% CO_2. Blood lactate levels remained low through hypothermic procedures when 5% CO_2 was used. Perfusion rewarming had little effect on lactate levels. The use of 100% O_2 resulted in slightly higher lactate levels, especially in the ether anesthetized group, but these levels still remained within the upper limit of the normal range. Significant differences in lactate levels between halothane and ether anesthesia suggest different mechanisms of tissue circulation and metabolism during hypothermia. Halothane anesthesia can be useful with the use of CO_2 for surface hypothermia with 30 minutes circulatory occlusion but is still inferior to ether.

As an adjunct to total repair of various congenital cardiac anomalies in infancy, surface induced deep hypothermia has been successfully utilized in our institution.[6-8] Ether has been used as an anesthetic but its explosive nature stimulated continuing search for better anesthetic drugs. Our previous experiment with halothane,[14] demonstrated definite inferiority of the drug to ether when administered in 100% O_2 with our hypothermic procedure.[12,13] Barratt-Boyes and associates,[2] however, have reported successful clinical trials of surface cooling-perfusion rewarming utilizing halothane anesthesia combined with carbon dioxide.

The current studies have been undertaken to evaluate effects of the use of carbon dioxide or perfusion rewarming during hypothermia on the period of total circulatory occlusion under halothane or ether anesthesia.

Materials and Methods

Twenty-five healthy adult mongrel dogs with an average weight of 17.5 kg were subjected to surface cooling, total circulatory arrest for 30 minutes and then rewarmed. In 15 of these dogs the anesthetic agent was halothane. Five dogs were ventilated with 100% O_2 and rewarmed by extracorporeal means (Group I). Five dogs were given a 95% O_2 and 5% CO_2 mixture and surface rewarmed (Group II), and the remaining five dogs were perfusion rewarmed with use of the same gas mixture (Group III). Ten dogs received ether anesthesia—five were given 100% O_2 and surface rewarmed (Group IV), and the rest received 95% O_2 and 5% CO_2 and were surface rewarmed (Group V).

The effects of CO_2 or perfusion rewarming on the dura-

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tion of safe circulatory occlusion were evaluated. Changes in blood pH, PaO_2, $PaCO_2$, glucose and lactate during various procedures were also studied.

Anesthesia

Anesthesia was induced by intravenous thyamylal sodium. Animals were then intubated and ventilation was maintained with a volume-constant mechanical ventilator. A non-rebreathing circuit was used for all halothane groups and the 5% carbon dioxide-ether group, and a closed circuit was applied for the 100% oxygen-ether group. A normal tidal volume for normothermia was maintained throughout the entire procedure. Anesthetic levels were maintained deep enough to eliminate shivering.

Hypothermia

Cooling was performed by immersion in ice water. When the rectal temperature reached 22 C, the animal was removed from the ice bath. The temperature eventually drifted down to an average of 18.3 C. During cooling from 35 to 25 C, 10% low molecular weight dextran in saline (10 ml/kg) was administered in surface rewarming groups, while the same volume of saline was given in pump rewarming groups. Through a right thoracotomy, cardiac arrest was accomplished by occlusion of inflow and outflow vessels and injection of Young's solution* into the aortic root. Resuscitation was accomplished by gentle cardiac massage following the release of inflow and outflow occlusion and calcium chloride injection in surface rewarming groups; in perfusion rewarming groups, partial bypass was used. A 50 volt AC shock was applied for cardiac defibrillation when necessary.

Surface rewarming was performed in a warm water bath (42 C) with a plastic sheet interposed until rectal temperature reached 35 C. Perfusion rewarming was begun immediately after release of circulatory occlusion and continued until rectal temperature reached 30 C, at which time the perfusion rewarming was discontinued and surface rewarming initiated.

For perfusion rewarming, an arterial cannula in the aorta and a single venous cannula in the right atrium were inserted after total body heparinization (300 unit/kg) and induction of cardiac arrest. A model 2-110 Bentley bubble oxygenator was used without an additional heat exchanger. The extra corporeal circuit was primed with 1500 ml of re-heparinized fresh ACD blood to which 27 mEq/l of sodium bicarbonate was added to bring blood pH to normal range. Water temperature to the built-in heat exchanger was adjusted to 40–42 C after reaching the perfusion rate of 100 cc/kg/min.

Blood Sampling and Measurements

Blood sampling and pressure monitoring catheters were inserted into the right atrium, inferior vena cava and abdominal aorta through the femoral vessels. Blood samples were collected at normothermia, 30 C, 25 C, at the end of cooling, after three minutes of cardiac massage following cardiac arrest (18 C), 25 C, 35 C during rewarming, and on the next morning. Arterial PO_2, PCO_2, and pH were determined with a Radiometer pH meter model 27. Temperatures of pH and blood gas electrodes were preadjusted to the aforementioned sampling temperatures in order to eliminate temperature correction. Blood glucose and lactate were measured by modified Brown and Bittner's[4] method and enzymatic fluorometric method[11] respectively.

Results

All dogs survived and were followed for at least three weeks. Postoperative neurologic sequelae and the course of hypothermic procedures are presented in Table 1.

Postoperative Neurological Disorders

All five dogs in halothane-100% O_2-perfusion rewarming group (Group I) developed moderately severe gait disturbance, affecting all extremities. In the halothane-5% CO_2-surface rewarming group, only one dog exhibited moderately severe high stepping gait and there were no abnormal dogs in halothane-5% CO_2-perfusion rewarming group. Both groups with 100% O_2 or 5% CO_2 under ether anesthesia and surface rewarming were normal. No dogs in any groups demonstrated any detectable sensory disturbance.

Course of Hypothermia

The cooling procedure was usually uneventful except for one dog of the halothane-5% CO_2 groups which developed ventricular fibrillation at 21 C during preparation for cirulatory occlusion. There were no significant differences in blood pressure or pulse rate during cooling between groups. The time required for cooling was similar in all groups, averaging 87 minutes. The halothane-CO_2 groups seemed to require much more anesthetic agent than the 100% O_2 group to maintain proper anesthetic levels.

At resuscitation, manual cardiac massage alone resulted in spontaneous resumption of cardiac beats in two of five dogs of the halothane-100% O_2 group and three of five dogs in all other groups. The rest developed ventricular fibrillation while cardiac massage was carried out, but the hearts were easily defibrillated with AC shocks. There was no significant difference in the ease of cardiac resuscitation between surface rewarming groups. The average time for successful resuscitation in both surface and

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* 0.81 gm of potassium citrate; 2.46 gm of magnesium sulfate; 0.001 gm of neostigmine methylsulfate; H_2O q.s. to 100 ml; pH adjusted to 7.4 with $NaHCO_3$.

TABLE 1. *Postoperative Neurologic Sequelae*

Exp. Group	No. Dogs	Body Weight (kg)	Anesth. Agents	Resp. Gases	Method of Rewarming	Vent. Fib. during Cooling	Spont. Resusc.	Motor Dist.	Duration of Cooling (min)	Duration of Rewarming (min)
Prev*	5	18.4 ±3.1	Halothane	100% O_2	Surface	0	4	5	80.0 ± 8.6	209.6 ±36.8
1	5	18.0 ±3.1			Perfusion	0	2	5	99.2 ± 9.0	134.8 ±19.2
2	5	18.0 ±3.1		95% O_2 and 5% CO_2	Surface	1	3	1	82.5† ± 8.8	208.2 ±20.4
3	5	17.2 ±2.2			Perfusion	0	3	0	83.6 ±22.2	225.6 ±37.6
4	5	18.3 ±2.5	Ether	100% O_2	Surface	0	3	0	84.0 ±16.9	179.6 ±27.6
5	5	16.3 ±2.2		95% O_2 and 5% CO_2		0	3	0	81.5 ±17.7	212.0 ±19.1

* Previously reported.
† Not including one fibrillated.

perfusion rewarming groups was between one and ten minutes, although resumption of myocardial activities with perfusion rewarming was much faster and more vigorous.

Perfusion rewarming provided a rapid increase in arterial blood pressure and core temperature. Total rewarming times required for pump warming to 30 C (rectal) were 61.0 minutes (3.4 min/kg) in the halothane-100% O_2 group and 77.0 minutes (4.5 min/kg) in the halothane-5% CO_2 group. With discontinuation of the perfusion rewarming both esophageal and rectal temperatures dropped 1 or 2 C and it required an additional 66.7 minutes (3.7 min/kg) in halothane-100% O_2 group and 164.2 minutes (9.5 min/kg) in the halothane-5% CO_2 group to rewarm to 35 C.

Surface rewarming was slower and blood pressure slightly lower as compared to perfusion rewarming groups at the initial phase of rewarming but progressed uneventfully without the administration of cardiotonic drugs. The arterial pressure during rewarming was lower in halothane groups than in the other group and more careful observation was required during rewarming.

Glucose and Lactate Levels in Blood

The alterations in blood glucose and lactate levels are ilustrated in Fig. 1 (halothane groups) and Fig. 2 (ether groups).

Halothane anesthetized groups showed a gradual but slight decrease in glucose levels as body temperature decreased. At resuscitation, perfusion rewarming groups demonstrated high glucose levels, apparently due to ACD blood use. While perfusion rewarming progressed, glucose levels tended to decrease in 5% CO_2 groups, but it tended to increase and reached 300 mg/100 ml at 35 C in the 100% O_2 groups. In the surface rewarming 5% CO_2 group, glucose levels remained unchanged at resuscitation and tended to increase during rewarming but to a minor degree.

Under ether anesthesia, glucose levels remained unchanged during cooling in the group with 100% O_2, while it gradually increased in the group with 5% CO_2. Glucose levels increased during rewarming in both 100% O_2 and 5% CO_2 groups and reached 230 mg/100 ml at the end of rewarming. The glucose levels during rewarming in ether group were slightly higher than those in the halothane and surface rewarming group.

Under halothane anesthesia, lactate levels increased slightly during cooling when ventilation was with 100% O_2, while with 5% CO_2 the levels tended to decrease. However, the highest lactate levels at 18 C during cooling were less than 2.5 mEq/l even when 100% O_2 was utilized. During rewarming, lactate levels in all groups gradually increased, the increase being slightly greater in the 100% O_2 group. The method of rewarming, either surface or perfusion, did not make any difference in lactate levels (Fig. 1).

Under ether anesthesia, lactate increased steadily during cooling from 1.5 mEq/l to 4.8 mEq/l when 100% O_2 was utilized. When 5% CO_2 was utilized, average lactate levels increased from 1.7 mEq/l (control) to 2.8 mEq/l (18 C) but showed wide individual differences. During rewarming from 25 to 35 C, the steady increase in lactate levels was noted in both 100% O_2 and 5% CO_2 groups reaching 8.2 mEq/l and 5.7 mEq/l at 35 C respectively (Fig. 2).

Blood Gas Analysis

Changes in pH, PaO_2 and $PaCO_2$ of three groups associated with 5% CO_2 use in the gas mixture are illustrated in Fig. 3. Changes in arterial PaO_2 and $PaCO_2$ were similar in all groups either with halothane-perfusion rewarming, halothane-surface rewarming or ether-surface rewarming except at the end of three minutes of cardiac massage where the halothane-surface rewarming group showed slightly lower arterial oxygen tension. Arterial pH, however, tended to stay low in the ether anesthetized group through the cooling and rewarming periods.

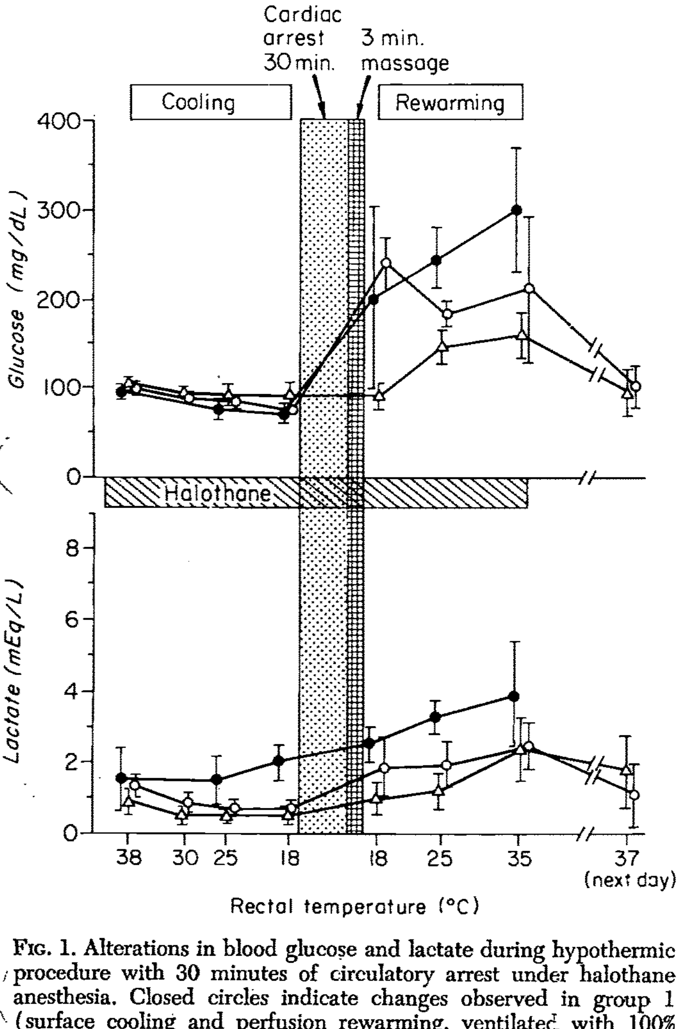

FIG. 1. Alterations in blood glucose and lactate during hypothermic procedure with 30 minutes of circulatory arrest under halothane anesthesia. Closed circles indicate changes observed in group 1 (surface cooling and perfusion rewarming, ventilated with 100% O_2.) Open triangles indicate changes observed in group 2 (surface cooling and surface rewarming with 95% O_2 and 5% CO_2.) Open circle indicate the changes in group 3, (surface cooling and perfusion rewarming with 95% O_2 and 5% CO_2) Mean value and one standard deviation (vertical bars) are plotted.

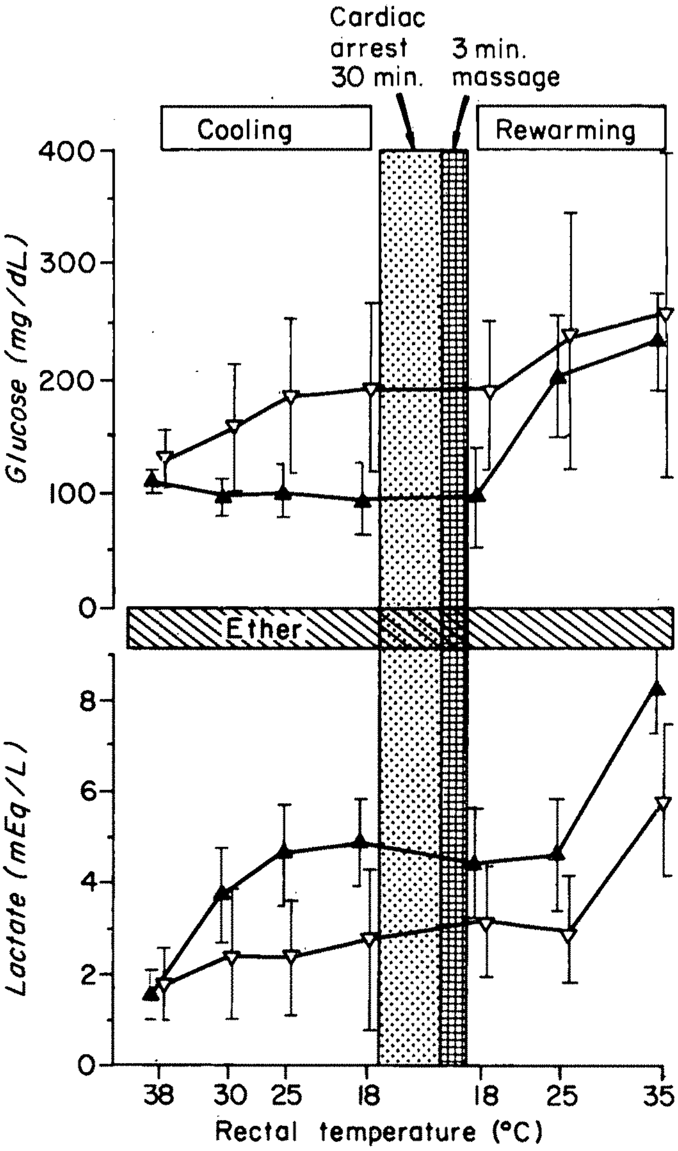

FIG. 2. Alterations in blood glucose and lactate during hypothermic procedure with 30 minutes of circulatory arrest under ether anesthesia. Closed triangles indicate changes in group 4 (surface cooling and surface rewarming, ventilated with 100% O_2.) Inverted open triangles indicate changes in group 5 (surface cooling and surface rewarming, ventilated with 95% O_2 and 5% CO_2).

Discussion

Previous experiments[14] in this institution have demonstrated the inferiority of halothane anesthesia to ether when utilized with surface hypothermia and 100% oxygen. Severe motor disorder resulted in the halothane group after total circulatory arrest for only thirty minutes while the motor disorder did not develop with the use of ether anesthesia.[12,13] Perfusion rewarming combined with surface cooling in an attempt to improve circulation during rewarming did not alter the outcome. The present study has demonstrated the mandatory use of CO_2 when halothane anesthesia is utilized. Addition of CO_2

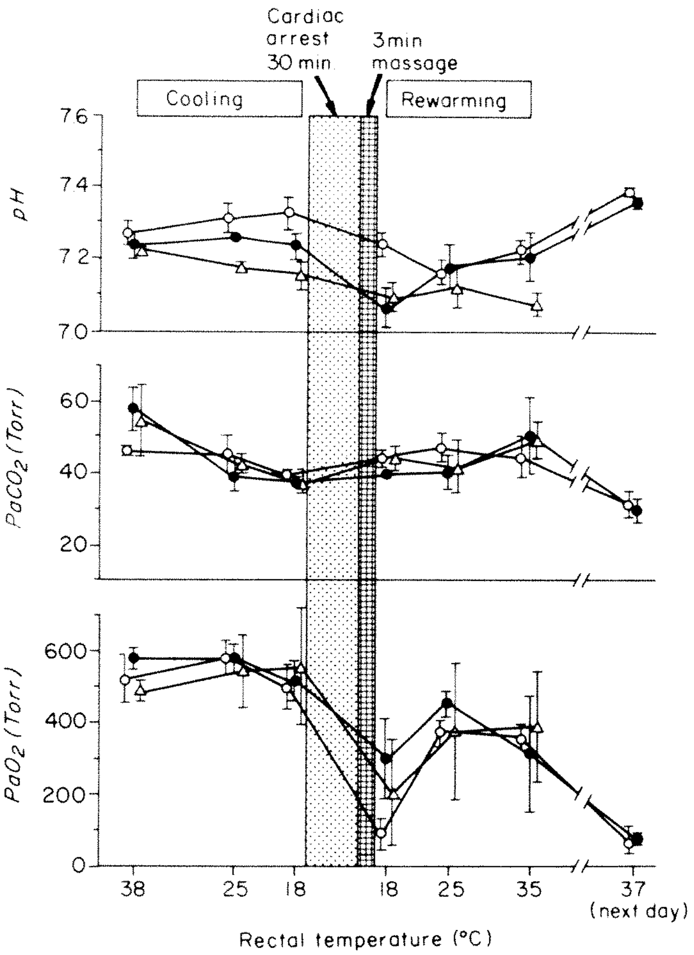

FIG. 3. Alterations in pH, PCO_2 and PO_2 during hypothermic procedure utilizing 95% O_2 and 5% CO_2. Open circles indicate the changes in group 2 (surface cooling and surface rewarming under halothane anesthesia.) Closed circles indicate the changes in group 3 (surface cooling and perfusion rewarming under halothane anesthesia.) Open triangles indicate the changes in group 5 (surface cooling and surface rewarming under ether anesthesia).

in the gas mixture theoretically improves oxygen transfer from blood to tissue. With ether anesthesia, oxygen transfer to tissue from blood seemed to be carried out even under severe alkalotic conditions without the use of CO_2. Such differences in oxygen transfer from blood to tissue under different anesthetics warrant further study.

Perfusion rewarming has theoretical advantages to surface rewarming[5,9,17] since it permits core organs to rewarm first and supports the circulation. Disadvantages of the use of perfusion procedures include difficulty of blood balancing, postoperative lung complications and hematologic disorders. However, in perfusion rewarming, postoperative bleeding and depressed respiratory function required somewhat prolonged respiratory support and were more pronounced than with surface rewarming. We therefore believe that surface rewarming still has advantages over perfusion rewarming at this time. The safe time limit for total circulatory occlusion associated with halothane-CO_2-perfusion rewarming needs to be explored.

The shorter rewarming time associated with perfusion rewarming is an advantage. Many institutions still use perfusion rewarming to 30 C and thereafter change to surface rewarming. In the present study surface rewarming from 30 C to 35 C required considerable time. Thus, it may be better to continue perfusion rewarming to 35 C while surface rewarming is applied concomitantly. The slight difference in serum lactate levels between halothane and ether anesthetized groups is apparently related to anesthesia. The use of 100% O_2 also resulted in slightly higher lactate levels during cooling. Although lactate levels remained at less than 8 mEq/l, there may be more depressed liver function or higher levels of anaerobic carbohydrate metabolism with the use of 100% O_2.[1,3,10,15] In lieu of the superior results associated with ether-100% O_2 utilization, it is difficult to understand the significance of higher lactate levels. Differences in blood flow distribution to various tissue, which may wash out metabolic products or variations in the mechanism of carbohydrate metabolism with different anesthetic agents are suspected.[16] At any rate, superiority of certain hypothermic methods should not be judged on the basis of difference in blood lactate levels, but should be evaluated by lesser morbidity and a longer safe circulatory occlusion time.

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Gardner's Syndrome:

Report of a Family

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Two cases of Gardner's syndrome in one family are presented. The father presented all three stigmas of the syndrome, while in the daughter no osseous manifestations were found. In the first patient, the diagnosis was made only after the second abdominal operation, when a mesenteric fibrous mass was seen. In the second case, the intestinal polyposis was clinically suspected, considering the hereditary aspects of this syndrome, and the episode of bloody diarrhea presented by this patient. Both patients were treated by subtotal colectomy with ileo-rectal anastomosis. Both of them presented fibrous tumors after the abdominal operation (the father after six years and the daughter after one year). The authors stress the importance of postoperative followup for the detection of fibrous masses that may appear due to the surgical stimulus. The literature on Gardner's syndrome is reviewed and summarized.

THE TRIAD of polyposis of the colon, benign osseous tumors and soft tissue masses, was first described by Gardner and his co-workers in a series of articles from 1950 through 1953.[9-12] In these papers, they presented six patients in a family group of 51 living persons, who proved to have the fully developed syndrome. The triad is known as the Gardner's syndrome, and since then some 200 cases of multiple polyposis of the colon, associated with hard and soft tissue tumors, have been reported.[17] This syndrome is inherited in a mendelian dominant pattern and is frequently incomplete; the colon polyposis may be associated with one or both of the extra-intestinal manifestations. The recognition of this syndrome is therefore important, because of the associated colonic malignancy.

Two cases of Gardner's syndrome in one family are described.

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Case Reports

B.D., a 37-year-old man was admitted in August 1965 to a medical ward in our hospital, complaining of watery diarrhea (up to ten times a day) for approximately one year, and a weight loss of 12 kg in this period. In the last month, fresh blood appeared mixed with the stool. In the past, he had a fracture of mandible in 1961, following a road accident.

At admission, the patient was pale, in a poor general condition, and clubbing of the fingers of the hands and feet was noted. The blood pressure was 130/90 mm Hg, the pulse was 94/min. The hemoglobin was 5.7 gm %, hematocrit 30%, serum proteins 5.6 gm/100 ml, iron 23 mcg/100 ml and potassium 2.8 mEq./l.

Ulcerative colitis was suspected, but the patient refused any investigation and left the hospital. He was told to take salazopirine, steroids, tranquilizers and ferum derivates at home.

After three weeks, he was readmitted to our hospital with the same complaints—watery bowel movements, associated with passage of bright red blood. The salazopirine and steroid treatment was continued, but this time a barium enema and rectosigmoidoscopy were done. The X-ray showed multiple polyps all over the colon (Fig. 1). At the proctoscopic examination, biopsy of polyps was done, and it showed benign adenomatous polyps. In view of these findings, in December 1965, a subtotal colectomy with ileorectal anastomosis was performed.

At the histologic examination of the colon, adenocarcinoma was found in one polyp from the cecal region. The postoperative course was uneventful and the patient was discharged three weeks after the operation.

On January 1971, he was again admitted to our department, this time with signs of intestinal obstruction. At the laparotomy, several adhesions were found, one of which occluded the small intestine, and lysis of the adhesions was performed. At the exploration of the abdominal cavity, in the root of the mesentery, a hard mass 8 cm in diameter with irregular margins was found. This mass was unremovable because it was firmly attached to the

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mesenteric vessels. Biopsy was performed and the histological examination showed "fibrous tissue" (Fig. 2). As two components of Gardner's syndrome were already present (colonic polyposis and fibrous mass in the mesenteric root), a radiographic bone survey was undertaken and exostosis of the right tibial bone was seen (Fig. 3). Therefore, the patient was diagnosed as suffering from Gardner's syndrome.

The postoperative course was uneventful, and the patient left the hospital in a good general condition.

At followup, in January 1973, eight years after the subtotal colectomy, at rectoscopy, three rectal polyps were seen and fulgurated. Biopsy from these polyps showed benign adenomatous polyp.

B.E., the 16-year-old daughter of the previous patient, had a period of bloody diarrhea in 1969, which cleared with oral medication. Considering the genetic character of the illness of her father, a barium enema was done, and multiple scattered polyps were seen over the entire colon. Rectoscopy and biopsy showed adenomatous polyp of rectum. As the rectal bleeding reappeared, and considering the malignant potentialities of the disease, surgery was decided. In December 1971, a subtotal colectomy with ileoproctostomy was done. The patient was discharged 13 days after the operation, with one to two loose bowel movements a day.

In January 1973, she was again admitted to our department, because three weeks earlier she remarked a mass in the region of the left breast. On examination, in the upper half of the left breast, a hard painless mass 10 cm in diameter was palpated, and felt to be adherent to the pectoralis muscle. Mammography was done and showed the mass to be beneath the mammary gland. The patient was operated on, and the mass was found to be beneath the mammary gland, adherent to the fascia of the pectoralis major muscle. The microscopic examination revealed a typical desmoid tumor (Fig. 4).

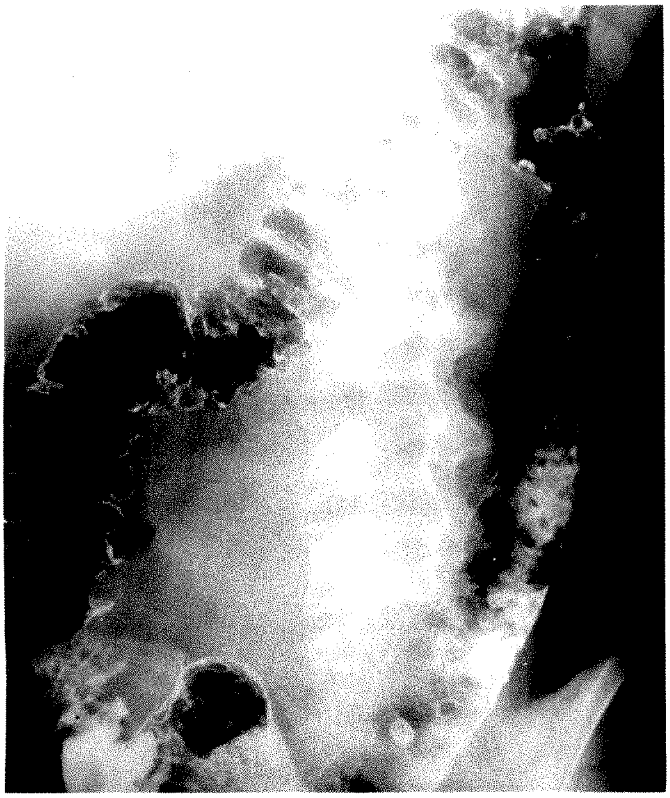

FIG. 1. Barium enema showing multiple colon polyps.

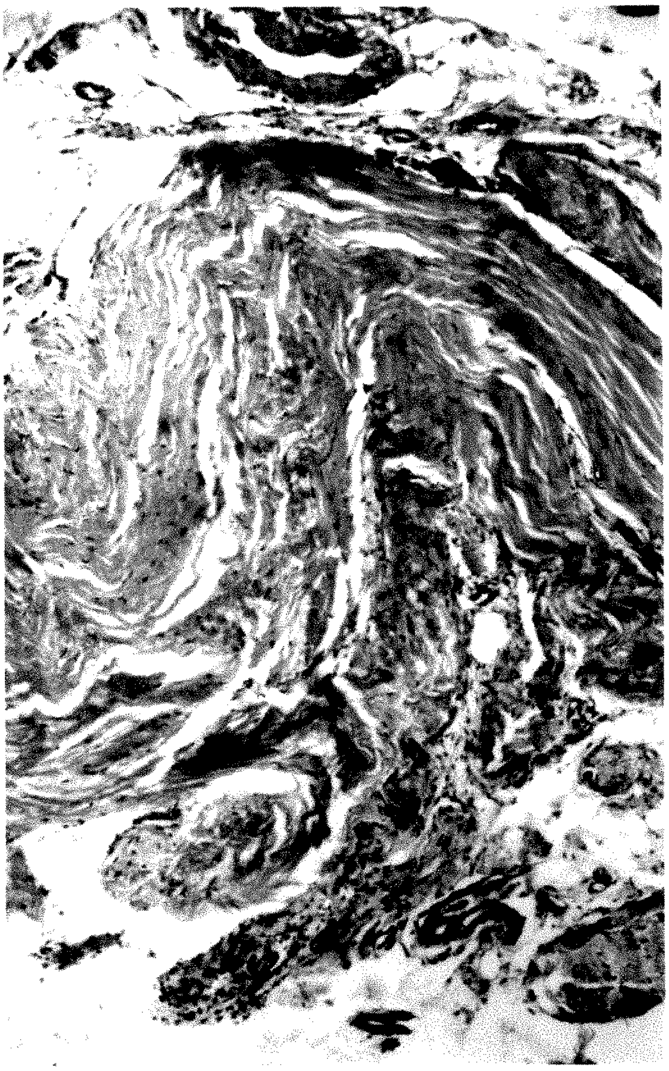

FIG. 2. Photomicrograph from the mesenteric fibrous mass (Case 1) shows collagen fibers and fibroblasts. The fibrosis often forms finger-like projections, anastomosing columns and moderately broad sheets that separate clusters of adult fat cells of the mesentery (H & E × 135).

The postoperative course was uneventful and the patient was discharged nine days after the operation.

Discussion

In Gardner's syndrome, the soft tissue tumors are usually mutiple. The most common ones are epidermoid cysts, sebaceous cysts, desmoid tumors, fibromas or poorly defined conective tissue tumors.[1,14] These may be found superficially, frequently in the postoperative scars, or in the mesentery of the small or large intestine.[23] In Gardner's syndrome there is an unusual tendency to fibrous proliferation. In addition to small tumor masses like fibromas or desmoid tumors, the excessive fibrous reaction may take a more diffuse form, infiltrating the

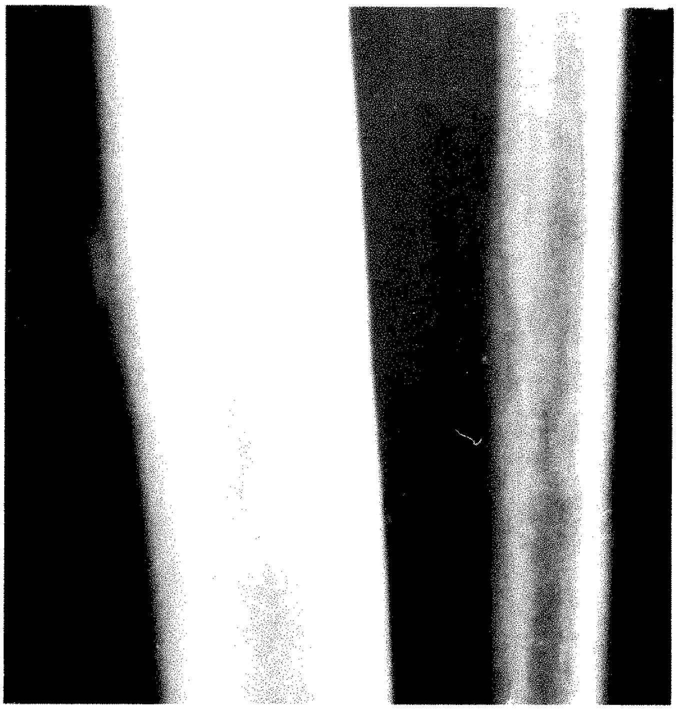

FIG. 3. Exostosis of the right tibial bone (Case 1).

mesentery, mesocolon or the retro-peritoneal tissues. A great amount of fibrous scar tissue and excessive adhesions have been found in many patients (as in our first patient). It is supposed that the fibrous mesenteric masses that appear are caused by the abdominal surgery, especially mesenteric surgery, performed in these patients.[13,24,25]

A particular type of fibromatosis that patients with Gardner's syndrome tend to form in their operative wounds and other areas, is the desmoid tumor.[26] This tumor arises from the connective tissue of muscle or fascia. These tumors are usually located in the anterior abdominal wall and many of them arise from the fibrous or aponeurotic structures. Desmoid tumors affecting the musculo-aponeurotic structures outside the abdominal wall are widely recognised.[4,6] The tumor has no true capsule. At the muscle border, the tumor extends in an infiltrative manner between muscle fascicles. The muscle remnants captured by the proliferating fibroblastic tissue, either undergo complete atrophy, or remain within the tumors multinucleated muscle giant cells.[18] Because of these characteristics these tumors continue to present a difficult problem in interpretation and management. Their pathogenesis remains unexplained, although certain factors seem to be important. Trauma, whether surgical or physiologic (as in labor) has been implicated, and desmoid tumor may appear as a reaction to a stimulus in a person who is genetically predisposed to react to such stimulation by excessive proliferation of cells of mesenchymal origin.[8,18] Gardner's study has shown that the soft tissue tumors may also develop in infancy and even in utero. In succeeding generations, five patients less than one year of age have been found to have subcutaneous tumors and one had multiple epidermoid cysts at birth. In the cases reported by Coli *et al.*,[4] one patient had a fibroma at birth and one developed an incisional desmoid in infancy.

The benign osseous tumors are benign osteomatoses or exostoses, consisting of bony proliferations of various size, from slight thickening to large masses. They are confined for the most part to the skull and facial bones. The mandible in particular is involved, so that many patients were first seen by dental surgeons.[4] Fader[7] believes that multiple impactions of supranummerary teeth are an additional diagnostic sign in this syndrome. In a number of cases, long bone manifestations had been seen. These

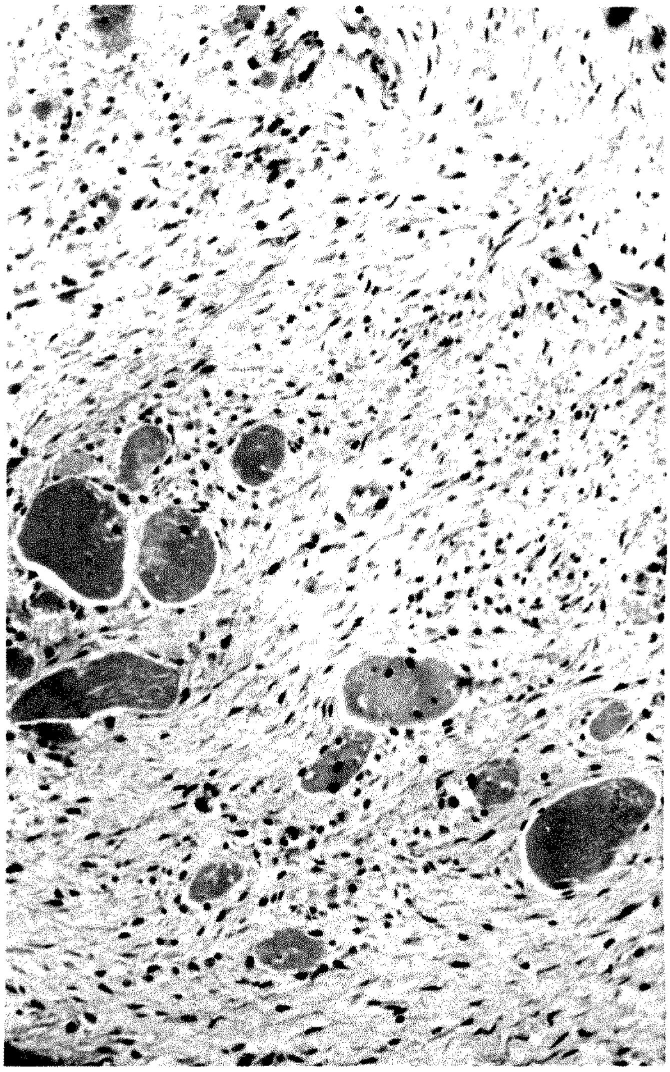

FIG. 4. Photomicrograph of the retromammary mass (Case 2). There is a dense fibrous stoma and fibroblasts. The engulfed muscle fibers appear as round bodies with a homogene acidophilic cytoplasm and a few picnotic nuclei (H & E × 135).

are self limiting and have not been reported as undergoing any malignant change [2]

The polyposis of colon is a hereditary disorder, consisting of multiple adenomas of the bowel, most commonly in the colon and rectum, and which have definite malignant potentialities. It is now generally accepted that this disease is transmitted as a heterozygous mendelian dominant, probably arising as a gene mutation. It is not sex-linked; it may be transmitted through either parent and a child of either sex can inherit it. Approximately 50% of the offspring are affected.

In cases without past familial history of polyposis, it is believed that the mutated gene may have been transmitted as a recessive trait, that there has been a lack of penetrance or expressivity in the parent with the mutant gene, or that the disease begun as a mutation in the individual under study.

McKusik[19] described the difference between the polyposis of Gardner's syndrome and familial polyposis: "The polyps of the colon in Gardner syndrome are multiple, but scattered. They do not carpet the colon as in familial multiple polyposis, and may occur anywhere in the length of the gastro-intestinal tract."[19]

This author believes that the gene which determines the Gardner's syndrome is unquestionably distinct from that of familial polyposis of the colon. His conclusion is based on the phenotypic differences, specifically the occurence of the osseous and soft tissue tumors and the distribution of polyps throughout the gastrointestinal tract in the Gardner's syndrome. He explained this resemblance by the fact that the genes for the two entities are allelic, that is, located at the same genetic locus.

In a more recent work, Pierce, Weisbord and McKusik[22] estimate the frequency of Gardner's syndrome gene at birth to be one in 14,025. They presented a family group, composed of 641 descendants of a couple, spanning six generations and 140 years, and found that 71 members manifested at least one component of the Gardner's syndrome triad: 37 had polyposis only, ten members manifested soft tissue abnormality only, and one kindred member showed bone abnormality only. Nineteen kindred members manifested two components; fifteen had soft tissue abnormality and polyposis, whereas four had polyposis and bone involvement. Only four kindred members exhibited the complete triad.

In most of the reported cases with this syndrome, the bone and soft tissue abnormalities precede the manifestations of the colonic polyposis.[5,13,14] In our cases, the colonic polyposis was the first manifestation of the syndrome.

The treatment of the polyposis of Gardner's syndrome is identical with the treatment of the familial polyposis. The indication for operation is absolute, whatever the age of the patient.

In the literature, a few patients are quoted, who were operated on at the age of five to six years. It is clear now that the colectomy performed at this age does not disturb the development of these children. Moreover, keeping in mind that those patients may present bloody diarrhea and consequently, anemia, the colectomy can only help their normal development. The best approach is therefore, the extirpation of the colon which is full of polyps. This operation excludes also the danger of malignant transformation of the polyps.

In the course of the last years, the subtotal colectomy with ileo-rectal anastomosis became the operation of choice, except when frank carcinoma exists at the time of the operation in one of the rectal polyps.[1,3,4,14,21] It is also important to preserve the rectum only when the polyps are not too numerous, so that their fulguration will not produce complications like perforation or strictures of the rectum. It is recommended[16] to fulgurate the polyps in more than one session, at 15-day intervals, and not to fulgurate on a region larger than one-fourth of the circumference of the rectum.

In our first case, some 15 polyps were fulgurated at the time of the colectomy. The patient has been seen in the followup clinic every three months, and now, eight years after the colectomy, three more polyps were extirpated and microscopically found as benign.

In the second case, at the operation, several polyps from the proximal rectum were also fulgurated, but many polyps in the distal part of rectum were left. When this patient was admitted for the second time, rectoscopy was done, and no polyps have been seen. This spontaneous disappearance of rectal polyps after the colectomy is mentioned more and more in the literature. Cole and Holden,[3] McLachlin,[20] Lambilliotte[15] described patients in whom rectal polyps disappeared after the colectomy. Lambilliotte,[15] on the histochemical studies of the remnant polyps, shows a significant decrease of their nuclear DNA content and of their mitotic activity. The author proposes three hypotheses to explain this regression:

1) The direct contact of the ileal content with the polyps (by changing the pH, or the bacterial flora).

2) The subtotal colectomy produces reduction of the blood supply to the rectum.

3) The existence of an intrisic factor, which is excluded together with the resected colon.

In view of these facts, it seems that the rectum has to be preserved when no evidence of carcinoma is found.

The soft tissue tumors, in general, are small, and local excision is usually sufficient, although mesenchymal tumors may sometimes recidive. In our first case, it was evident that the mesenteric fibrous mass did not exist at the first operation; it appeared afterwards. The fact that this mesenteric mass and the desmoid tumor of the second patient appeared both after surgery, stresses the importance of the repeated postoperative checkups. Besides the proctoscopic examination of the rectal stump, the appearance of fibrous masses (mesenteric or extra-abdominal fibrous tumors) triggered by the surgical trauma, should be looked for.

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Relationship of Plasma Aldosterone Concentration to Electrolytes and Acid-base Balance in Blood after Open Cardiac Surgery

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Plasma aldosterone concentration was measured in 11 cardiac patients after open cardiac surgery, by the radioimmunoassay method, and the relationship of it to electrolytes and acid-base balance of blood was analyzed. Plasma aldosterone concentration was markedly elevated in patients with low cardiac output, who required postoperative drip infusion of Isoproterenol, and in addition, both remarkable metabolic alkalosis and increase of potassium excretion in urine were confirmed in these patients. Plasma aldosterone concentration correlated significantly with potassium excretion in urine and was inversely related with potassium balance. However, plasma potassium concentration or arterial pH had no correlation to it. Approximately an inverse correlation was found between the logarithm of the sodium/potassium ratio in urine and plasma aldosterone concentration. These data indicate that aldosterone is an important factor which produces potassium depletion after open cardiac surgery.

POTASSIUM DEFICIENCY or hypokalemia associated with metabolic alkalosis following open cardiac surgery has been reported by several authors. This metabolic abnormality occasionally provokes postoperative arrhythmia that may result in death. These metabolic changes are assumed to be related to the dilution effect of the blood following extracorporeal circulation,[11,21] intracellular shift of potassium ion,[16,21] respiratory alkalosis[10] or increased aldosterone secretion.[13] The exact mechanism involved, however, is not yet clear. In the seriously ill cardiac patients with postoperative low cardiac output, it is not unusual to find severe metabolic alkalosis with marked potassium deficiency after open cardiac surgery.[17] This hemodynamic alteration stimulates the renin-angiotensin-aldosterone system and increases the release of aldosterone from the zona glomerulosa of the adrenal cortex.[7,8] It can be therefore postulated that the disturbances of electrolyte contents and acid-base balance in the blood are induced by increased release of aldosterone under this condition.

This study was designed to determine the relationship of aldosterone concentration in plasma to electrolyte contents and acid-base balance following open cardiac surgery.

Method

The present study included 11 cardiac patients. The ages of those who underwent open cardiac operations ranged from 19 to 46 years. These patients were divided into two groups. One group (Group A) included moderately ill patients who had a short perfusion time and had uneventful postoperative recoveries. Another group (Group B) included seriously ill patients who underwent a long perfusion and showed low cardiac output following operation. (Table 1). These patients required the drip infusion of Isoproterenol 1.5 μg/min to 0.1 μg/min during investigation. The content of electrolytes solution given intravenously during this period was as follows: 4.3% glucose, Na^+ 35mEq, K^+ 20mEq, Cl^- 35mEq and lactate 20mEq in 1000 ml of water. The amount of administered fluid ranged from 1000 to 1400 ml/M^2/day beginning 24 hours after operation.

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TABLE 1. *Investigated Cases and Perfusion Time*

Group A				Group B			
Disease	Age	Sex	Perfusion Time	Disease	Age	Sex	Perfusion Time
1) ASD	46	F	48 Min.	1) ECD	25	F	100 Min.
2) ASD	28	F	54	2) ECD	32	F	90
3) ASD	30	M	36	3) AI(AVR)	48	F	208
4) ASD	19	M	30	4) AI(AVR)	25	M	167
5) ASD + PS	30	F	48	5) AI(AVR)	42	M	315
				6) MI(MVR)	28	M	121
			43 ± 10 Min.				167 ± 85 Min.

AVR: Aortic Valve Replacement MVR: Mitral Valve Replacement

In Group B, potassium chloride (10 to 20 mM) was added when significant negative balance of potassium was found, and Furosemide of 10 to 20 mg was administered intravenously when the output of urine was decreased below 20 ml/h.

Since Group A could take oral diet from second or third postoperative day, the amount of intravenous infusion of electrolytes solution was gradually tapered and finally discontinued. However, in Group B, the oral intake of diet was usually impossible for about one week after operation. In addition, the patients of Group A could maintain spontaneous breathing whereas Group B required the mechanical respirator at least for the first two days after operation.

The investigation was performed every other day from 24 hours to seven days after operation. The result was 20 (N = 20) in Group A whereas it was 21 (N = 21) in Group B as isoproterenol was not required on the first and seventh postoperative day in case 2 and on the first day in case 6 and each parameter was not evaluated on these days (Table 1).

The arterial blood was obtained anerobically by femoral arterial puncture, and urine was collected for 24 hours on the day of examination. Arterial blood pH and pCO_2 was measured by a glass electrode (Radiometer Type BMS-2) and Severinghaus electrode (E 5037) at 37 C.

Base Excess (B. E.) values were calculated from Siggaard-Andersen nomogram and hematocrit values of the blood.[26] Plasma aldosterone concentration was evaluated by radioimmunoassay method of Mayes and co-workers.[22] The normal value was 8.7 ± 6.5 (0.9–20.1) ng/100 ml of plasma. Sodium and potassium concentration in plasma and urine were measured by flame photometer. The amounts of potassium and sodium loss in urine, sodium/potassium ratio in plasma and urine were calculated from the measured sodium and potassium values and urinary volume for 24 hours.

In Group B, potassium balance was calculated from amounts of potassium intake and loss. On the calculation of sodium and potassium loss and potassium balance, the results came to 19 (N = 19) because its estimation could not be performed on the fifth day in case 2 and seventh day in case 6. The statistical analysis was attempted by student's test with $p = 0.05$ as the level of significance.

Results

The plasma aldosterone concentration was significantly higher in Group B than in Group A (Group B: 8.6–132 ng/100ml. Group A: 0.5–38 ng/100 ml of plasma), (Table 2, Fig. 1). The higher arterial pH and BE values showed the metabolic alkalosis in Group B, whereas these values remained in the nearly normal range in Group A (Table 2, Fig. 2). Although the average values of arterial pCO_2 were distributed in the normal range in both groups, the moderately high values of arterial pCO_2 were occasionally found in Group A (Fig. 2). Average of potassium concentration level of the plasma was higher in Group B (Table 2) despite the increased aldosterone concentration in plasma. A remarkable difference of plasma sodium concentration was not seen among them (Table 2). Sodium/potassium ratio in plasma was less in Group B than in Group A (Table 2). Potassium loss in urine was greater and sodium loss was less in Group B than in Group A (Table 2). Average value of sodium/potassium ratio in urine was significantly lower in Group B (Table 2). As far as the relationship of aldosterone concentration to arterial pH or to plasma potassium concentration was concerned, there was no correlation between them in Group B (Fig. 3, 4); however, a significant correlation was found between plasma aldosterone concentration and the amount of urinary potassium loss, and thus far an inverse correlation existed between aldosterone level in plasma and potassium balance in Group B (Fig. 5, 6). The logarithm of sodium/potassium ratio in urine and aldosterone concentration in plasma has shown approximately an inverse correlation (Fig. 7).

Discussion

Aldosterone secretion increases temporarily for a few days following operation,[15] and the mild metabolic alkalosis is common in the uneventful postoperative course.[20,23] Our data, however, indicated significant high levels of plasma aldosterone and marked metabolic alkalosis with increased potassium loss in urine of patients with low cardiac output in comparison with those with-

TABLE 2. *Summary of Measured and Calculated Values*

	Group A		Group B		
Plasma Aldosterone Concentration (ng/dl)	N = 20	13.3 ± 9.3	N = 21	51.5 ± 34,6	$P < 0.001$
Arterial Blood PH	N = 20	7.429 ± 0.027	N = 21	7.484 ± 0.038	$P < 0.001$
Arterial P CO_2(mmHg)	N = 20	41.9 ± 6.5	N = 21	40.3 ± 4.3	$P < 0.4$
Base Excess (mEq/l)	N = 20	+2.8 ± 2.5	N = 21	+6.2 ± 3.0	$P < 0.001$
Plasma Potassium Concentration (mEq/l)	N = 20	3.8 ± 0.3	N = 21	4.3 ± 0.9	$P < 0.05$
Plasma sodium Concentration (mEq/l)	N = 20	136.8 ± 3.7	N = 21	137.3 ± 6.1	$P > 0.5$
Plasma Sodium/Potassium Ratio	N = 20	36.7 ± 3.6	N = 21	32.9 ± 6.0	$P < 0.02$
Excreted Potassium Amounts in Urine (mEq/kg/day)	N = 20	0.94 ± 0.46	N = 19	1.56 ± 0.61	$P < 0.001$
Excreted Sodium Amounts in Urine (mEq/kg/day)	N = 20	3.89 ± 1.84	N = 19	2.43 ± 1.58	$P < 0.01$
Sodium/Potassium Ratio in Urine	N = 20	5.1 ± 2.8	N = 21	1.9 ± 1.5	$P < 0.001$

out it. It suggests that this significant increase of aldosterone secretion is ascribable to the enhanced activity of renin-angiotensin-aldosterone system due to diminished renal perfusion resulting from low cardiac output.

In addition, the secretion of aldosterone is dependent upon sodium and potassium concentration in plasma.[9] Blair-West *et al.*[2] have reported that the increase of potassium concentration and a decrease of sodium concentration in renal cortical arterial blood stimulated the secretion of aldosterone in sheep. Weidman *et al.*[28] have shown a parallel correlation between plasma aldosterone concentration and plasma potassium level in terminal renal failure, and further, Cannon *et al.*[4] have pointed out that potassium administration stimulated aldosterone

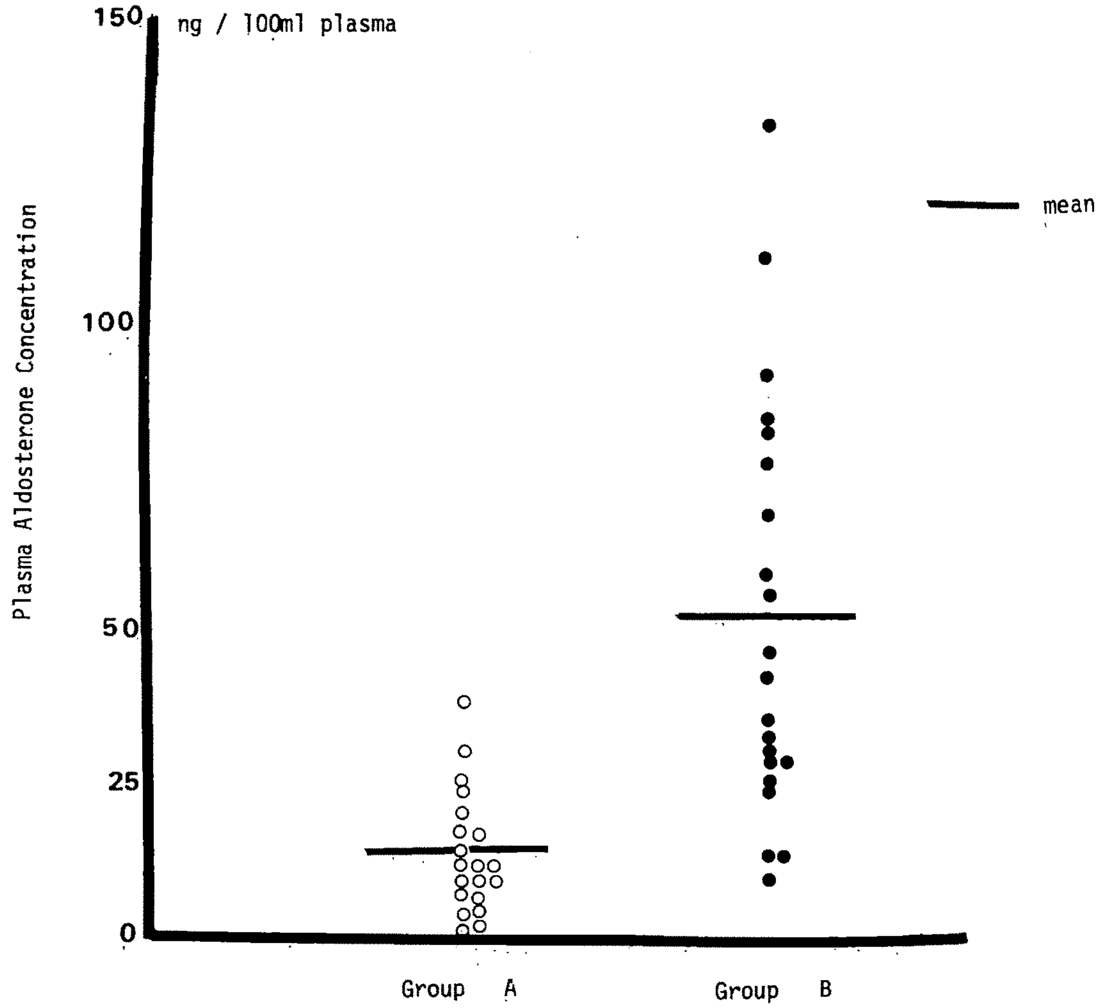

FIG. 1. Plasma aldosterone concentration in Group A and B.

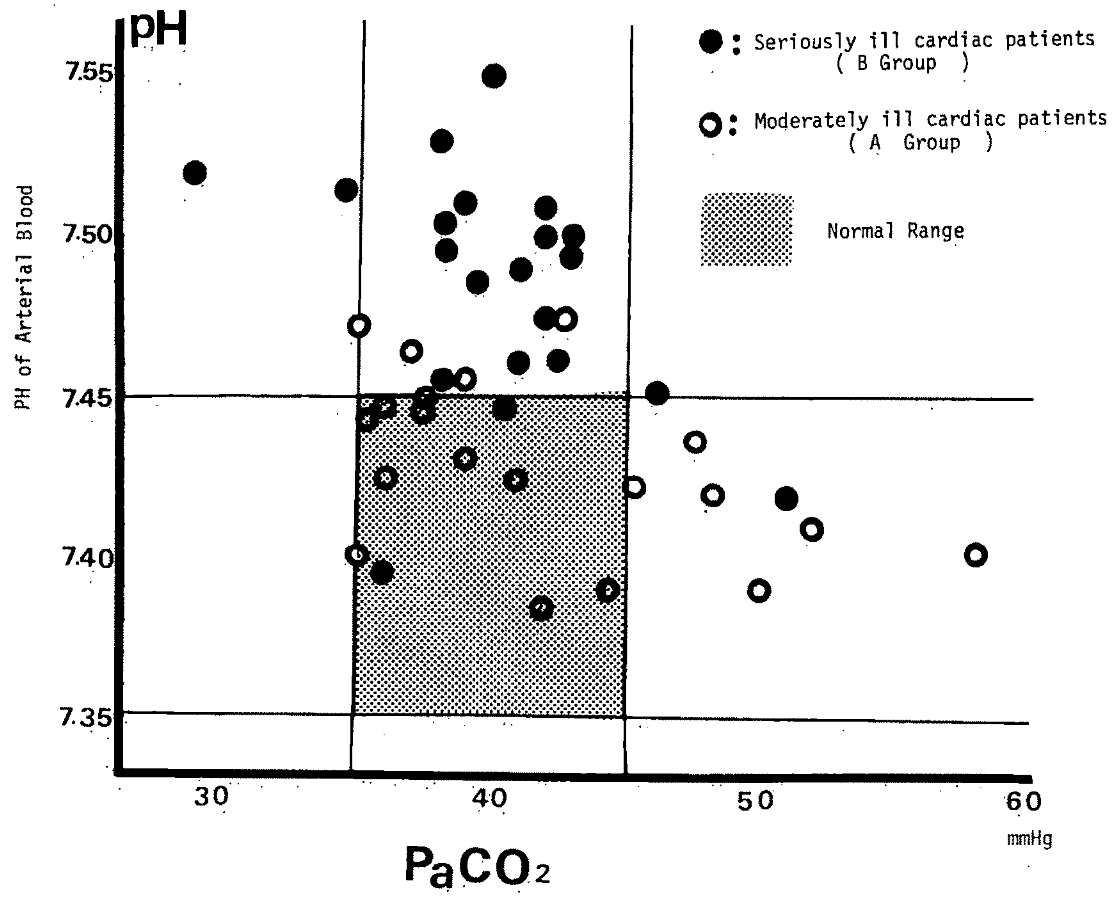

FIG. 2. Relationship between arterial pH and carbon dioxide tension in both groups.

secretion even when the plasma potassium level remained in normal range. However, Llaurado *et al.*[19] have reported that postoperative increase of potassium in the blood did not stimulate aldosterone secretion.

Our data indicated no correlation between potassium and aldosterone concentration in plasma of seriously ill cardiac patients (Fig. 4), but the concentration of potassium and aldosterone in plasma was higher than those

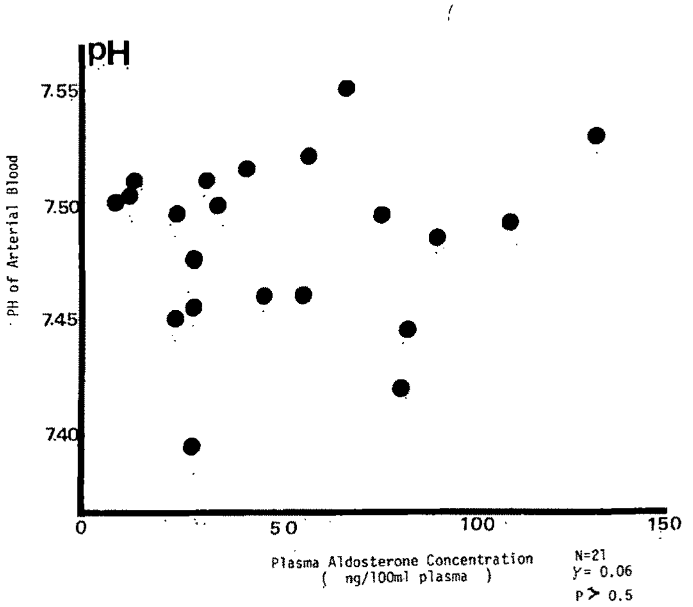

FIG. 3. Relationship between plasma aldosterone concentration and arterial pH in Group B.

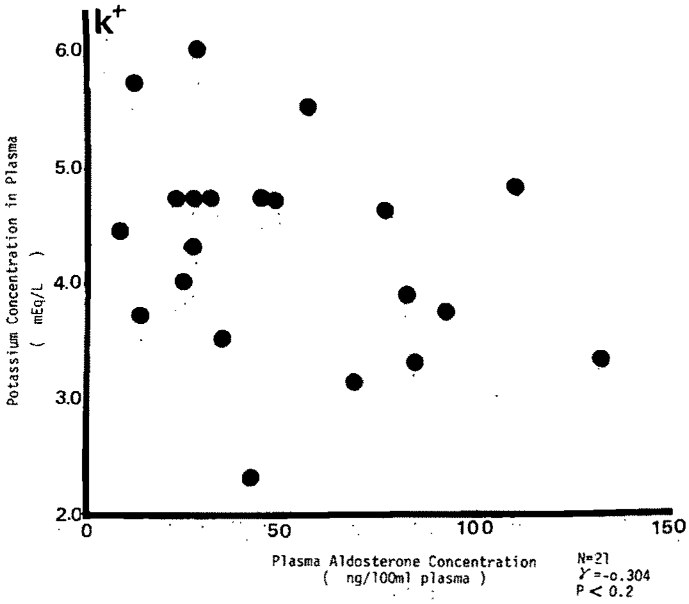

FIG. 4. Relationship between plasma aldosterone concentration and plasma postassium concentration in Group B.

in moderately ill cardiac patients. Therefore, the influence of potassium on aldosterone release could not be entirely ruled out in our data. The decrease of plasma sodium concentration has been known to stimulate the aldosterone secretion. This factor however can be negligible, because there was no difference of sodium concentration level of plasma in both groups (Table 2). Isoproterenol was administered by continuous drip infusion during investigation in seriously ill cardiac patients, and this drug seems to augment indirectly the release of aldosterone via increased renin secretion.[6,27] Administration of diuretic drugs, thus far, stimulate indirectly the secretion of aldosterone. Espiner *et al.*[12] have reported that administration of diuretics augmented aldosterone secretion in the patients without apparent edema.

It is, therefore, expected from this evidence that Isoproterenol and diuretic drug may partially stimulate the secretion of aldosterone in patients.

Pharmacological effect of aldosterone is known to augment reabsorption of sodium, secretion of potassium and hydrogen ion from the renal distal tubles. Our data have clearly shown decreased sodium excretion and increased potassium loss in urine in seriously ill cardiac patients with metabolic alkalosis (Table 2). Although administration of potassium chloride augments the amount of potassium loss in urine,[4] there was a positive correlation between plasma aldosterone concentration and the degree of potassium loss in urine or inverse relationship to potassium balance. This fact suggests that potassium loss is actually dependent upon aldosterone release at least under these disturbed hemodynamic states.

Although the significant increase of potassium loss was found in severely ill cardiac patients, plasma potassium remained at higher level than in mildly ill cardiac patients (Table 2). This phenomenon may be due to the increased somatic protein degradation[5] during postoperative malnutrition, potassium chloride administration and the increased hemolysis[3,29] caused by long perfusion

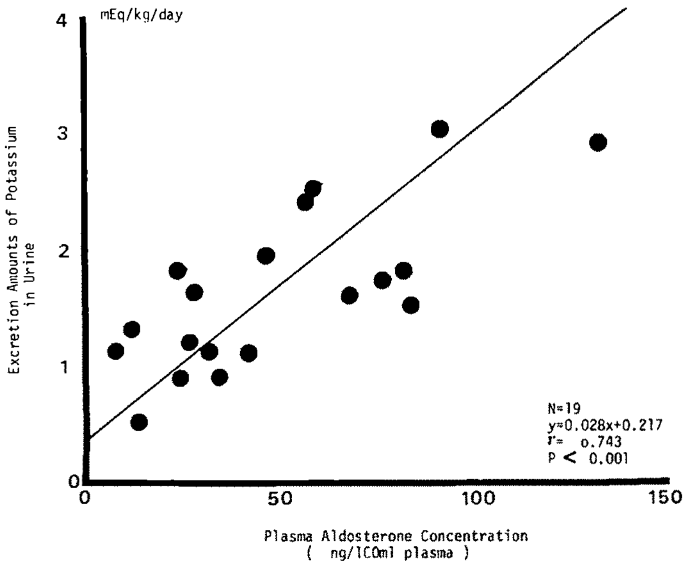

FIG. 5. Correlation between plasma aldosterone concentration and excreted amount of potassium in urine (Group B).

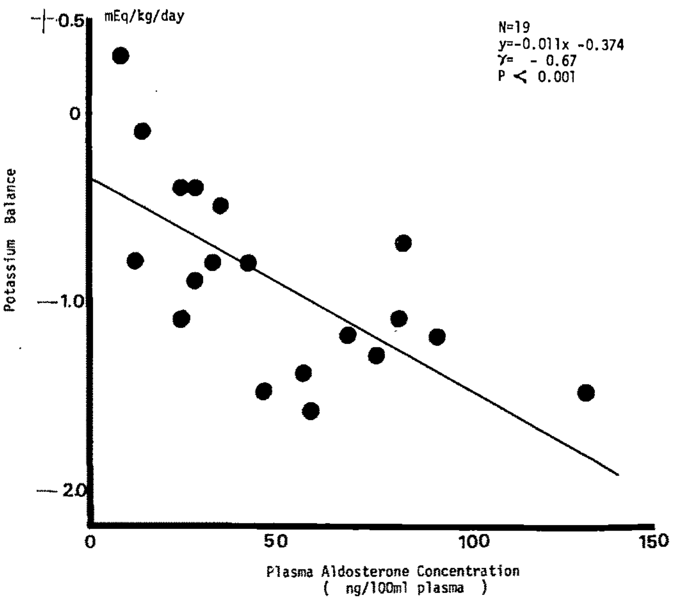

FIG. 6. Correlation between plasma aldosterone concentration and potassium balance in Group B.

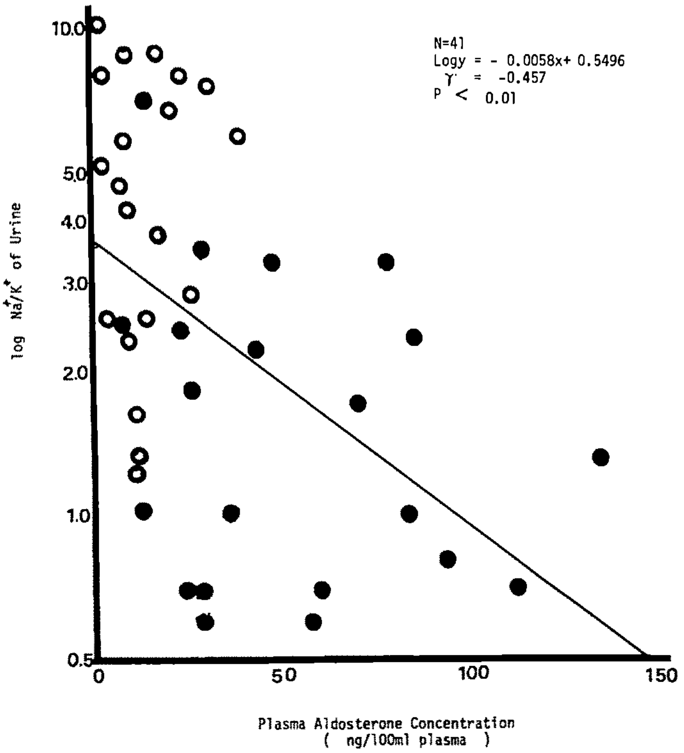

FIG. 7. Correlation between plasma aldosterone concentration and sodium/potassium ratio (logarithm) of urine in both groups.

(Table 1). These results indicate that the plasma potassium level does not always reflect the real total potassium balance.

Aldosterone increases hydrogen ion excretion from renal distal tubles and this action also induces metabolic alkalosis. However, no clear correlation was confirmed between aldosterone concentration and arterial pH in our present study (Fig. 3). It is suspected that the acid-base balance of blood is influenced by intracellular substances or carbon dioxide tension of blood. These factors, therefore, may affect the increase of blood pH due to hormonal effect of aldosterone. Urinary sodium/potassium ratio indicates a indirect index of aldosterone secretion.[24] Llaurado *et al.*[18] have reported that the logarithm of urinary sodium/potassium ratio showed a linear relation to aldosterone activity. However, this ratio is altered by glomerular filtration or glucocorticoid,[25] or diuretics.[14] Bland[1] pointed out that urinary sodium/potassium ratio showed not a linear but a mere approximate correlation with aldosterone activity. Our data have indicated similar results to those stated by Bland.[1]

In the present study, the results have shown a significant increase of aldosterone release in low cardiac output which has been compensated by the administration of an adrenergic agent after open cardiac surgery, and this hormone caused potassium depletion with metabolic alkalosis. As these abnormal metabolic changes induce a reciprocal vicious circle, the adequate plan of clinical therapy should be made on the basis of these fundamental alterations.

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Subphrenic Abscess:

Comparison Between Operative and Antibiotic Management

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Subphrenic abscess is still a significant hazard which complicates surgical procedures as well as certain abdominal catastrophes. This is a report of 88 patients with subphrenic abscess at St. Vincent's Hospital and Medical Center of New York from 1954 through 1971. There were 46 males and 42 females, ranging from 2 to 88 years. Operations on the stomach, duodenum and biliary tract were the major causes. The causative organisms in order of frequency were: *E coli* (41.6%), Staphylococcus (41.6%), *Aerobacter aerogenes* (23.3%), Proteus (20%), Streptococci (18.3%) and Pseudomonas (8.3%). Penicillin and tetracycline, the antibiotics most commonly chosen on an empiric basis, proved effective in only 38% of cases. On the other hand, kanamycin, chloramphenicol and cephalothin were effective in 90%, 85% and 70% of cases respectively. The overall mortality rate was 15%. Nine of the 21 patients (42.8%) treated with antibiotics alone died while 11 of 67 patients (10.6%) treated with antibiotics and surgical drainage died. Some of the latter deaths occurred in patients treated with prolonged antibiotic therapy and operated on only as a last resort. In this series subphrenic abscess was best treated by early surgical drainage combined with the use of appropriate antibiotics.

DESPITE THE ADVANCED KNOWLEDGE in postoperative care and diagnosis, subphrenic abscess is still a significant hazard which complicates the outcome of surgical procedures as well as other nonsurgical entities. The use of antibiotics has not changed the incidence of this complication as compared to preantibiotic experience and the diagnosis is at times more difficult when symptoms and signs are masked by these drugs.[2,4] This is a reappraisal of the part antibiotics has played in the management of this complication in our hospital.

Material and Methods

This series consists of 88 patients with subphrenic abscess who were treated at St. Vincent's Hospital and Medical Center of New York between 1954 and 1971. There were 46 males and 42 females. Their ages ranged from 2 to 88 years, with the majority of patients in the fifth, sixth and seventh decades of life (Table 1).

Location

Abscesses on the right were predominant (63.6%). Twenty-six per cent were found on the left side while 4.5% occupied the lesser sac. Abscesses in more than one space were treated in 5.7% of cases (Table 2).

Etiology

Abscesses complicating procedures performed on the upper abdomen were predominant. Figure 1 compares our series with that of Oschner and DeBakey's published in 1938.[6] An important contrast is noted. In our series the upper gastrointestinal tract and the liver each accounted for over 30% of the abscesses. In their series, the appendix was the major offender accounting for 31%, whereas this was the cause of only 10% of the abscesses we saw. As more elective surgery is performed in the

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TABLE 1. *Age Distribution*

Age (Year)	No.
1–10	1
11–20	1
21–30	6
31–40	13
41–50	17
51–60	18
61–70	21
71–80	8
81–90	3
Total	88

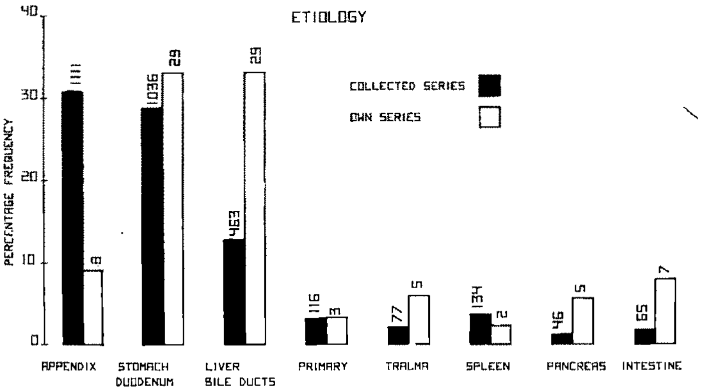

FIG. 1. Comparison of our series (white bars) with that presented by Oschner and DeBakey in 1938 (black bars). The number of patients studied in each series is found on top of each bar. We have found more abscesses complicating upper abdominal procedures as opposed to the higher incidence following appendiceal disease in the 1938 series.

upper abdomen and as more early and accurate diagnosis of appendiceal disease is made, more subphrenic collections are found as complications of procedures on the gastroduodenum and biliary passages.

Trauma to the abdomen accounted for 5.6% of cases. Three patients in this series developed subphrenic purulent collections as a complication of bronchopneumonia. All three patients were seriously ill and presented with septicemia. Positive cultures were obtained from blood, urine and cerebrospinal fluid. The remainder were postoperative abscesses complicating elective surgery of the pancreas, intestines and spleen.

Diagnosis

Pain and fever were constant findings in all patients. These findings were accompanied by tachycardia and leukocytosis. The erythrocyte sedimentation rate was elevated in 50% of cases. Eighty-seven per cent had pain. In most instances it involved the abdomen as well as the thorax.

On physical examination abdominal distention was observed in 59% of patients. Abdominal muscular rigidity or guarding was encountered in 71% of cases. Abnormal auscultatory findings, mostly consisting of rales and dullness located in one, or both, of the lower pulmonary areas were noted in two-thirds of patients.

Percutaneous diagnostic puncture of a subphrenic abscess was performed early in the study on two cases. These punctures did not contribute to the diagnosis and were rapidly followed by empyemas. We do not recommend this dangerous and blind procedure as a means to document a subphrenic collection.

Bacteriology

The great majority of abscesses cultured more than one organism (Table 3). Gram negative bacteria were predominant: *E. coli* (41.6%); *Aerobacter aerogenes* (23.3%); Proteus, (20%); and Pseudomonas, (8.3%). In recent years, Pseudomonas, rarely found in earlier studies, has become one of the most frequently cultured bacteria.

Gram positive organisms (Staphylococci, 41.6%; Streptococci, 26.6%) were also cultured with increasing frequency. These gram positive bacteria, which contaminate almost every abscess have become, through the years, resistant to the available antibiotics.

Thirteen patients (14.8%) had only negative cultures. These patients had been treated with massive doses of antibiotics for prolonged periods of time with no relief of symptoms. Upon drainage, all these patients had large purulent collections, apparently rendered sterile by

TABLE 2. *Location (In Order of Frequency)*

	No.	Percentage
Right Inferior	27	30.7
Left	23	26.2
Right Anterior	20	22.7
Right Posterior	9	10.2
Multispace	5	5.7
Lesser Sac	4	4.5
Total	88	100

TABLE 3. *Bacteriology*

E. coli	41.6%
Staphylococci	41.6%
A. Aerogenes	23.3%
Proteus	20%
Streptococci	18.3%
Pseudomonas	8.3%
Negative cultures	14.8%

the antibiotics. All recovered without sequellae after drainage.

Sensitivity studies were obtained in all positive cultures (Fig. 2). Comparing these sensitivities and the frequency with which these antibiotics were used, the initial antibiotic proved to be a poor choice in the majority of cases. While the cultured organisms were highly sensitive to kanamycin (90%), chloramphenicol (85%), and cephalothin (70%), these antibiotics were used in 6%, 41%, and 25% of cases. Penicillin and tetracycline, most commonly chosen on an empiric basis, proved effective on cultures in only 38% of cases. The most effective antibiotic for Pseudomonas infection was colimycin.

Radiological Studies

The most helpful radiological study proved to be a plain film of the chest. Pleural effusion was present in 70% of cases, pulmonary consolidation in 42%, elevation of the diaphragm in 56%, and air fluid level in 40%. All subdiaphragmatic abscesses caused intrathoracic changes; of the subhepatic abscesses, 30% caused no intrathoracic pathology. During the fluoroscopy, decreased motion of the diaphragm was seen in 25% of patients. Ileus was observed in 25% of patients. Upper gastrointestinal contrast studies, when indicated, helped to localize the position of the purulent collections.

As previously reported from our institution,[9] combined liver-lung or spleen-lung radioisotope scans as well as celiac or selective hepatic arteriography have helped to diagnose and localize a subdiaphragmatic purulent collection.

Treatment and Results

Every effort was made to drain the abscesses without entering the pleural or peritoneal cavities.

Although various spaces have been described[1,8,10] within the subphrenic region, we tried to group our patients according to the areas where the abscesses occurred. Thus we recognized purulent collections as occupying on the right: an anterior and a posterior subphrenic-suprahepatic space and an inferior (subhepatic) area. On the left, a single space was recognized and four abscesses were found within the lesser sac. All right posterior abscesses were drained through the bed of the twelfth rib following the principles described by Nather and Ochsner.[5,7] Fourteen right anterior abscesses were drained through the subcostal approach of Clairmont.[3] One left-sided collection was drained transpleurally inadvertently. All other surgically treated abscesses were drained through an exploratory laparotomy, sometimes using the primary incision. A last case was treated by using both transpleural and transperitoneal approaches.

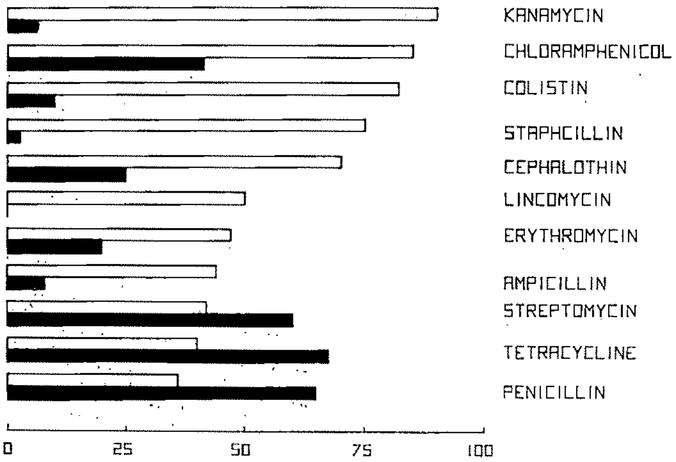

FIG. 2. Comparison of the percentage frequency of sensitivity of the cultured bacteria to the various antibiotics (white bars) against the percentage frequency with which these antibiotics were used (black bars).

The overall mortality rate was 23%. Nine of the 21 patients treated with antibiotics alone died (43%). Eleven of 67 patients (16%) treated with antibiotics and surgical drainage died (Table 4). Some of the latter deaths occurred in patients treated with prolonged antibiotic therapy and operated on only as a last resort.

Discussion

The widespread use of antibiotics has, by no means, simplified the problems associated with the diagnosis and management of a subphrenic abscess.[2,4] Signs and symptoms are often masked by these drugs and their continued use has lead to chronicity and might be responsible for the appearance of new, highly-resistant, bacteriologic forms.[8]

Although the surgical mortality reported in recent series has not substantially changed from that of almost 40 years ago,[2,6] it doubles when antibiotics alone are used to treat subphrenic abscesses. Antibiotic treatment alone, in our hospital, resulted in a prohibitive mortality. Antibiotics, however, have been utilized for many years. They may abort a subphrenic cellulitis before it becomes purulent and have allowed delay in drainage in the very ill.[8] When no bacteriological confirmation is available, the drug to be used should be one that will be effective against those organisms most commonly expected to be found in this complication. Penicillin, tetracycline and

TABLE 4. *Results of Treatments*

Treatment	Patients	Deaths	Percentage
Non Operative	21	9	43
Operative	67	11	16
Totals	88	20	23

streptomycin can no longer be considered the agents of choice. Kanamycin, chloramphenicol and cephalothin, in appropriate dosage, are able to cover the bacterial spectrum found in subphrenic abscess. While some abscesses may respond to antibiotics alone, the mortality noted in our series makes this a dangerous method of treatment. When a subdiaphragmatic purulent collection has been established, early surgical drainage is the only definitive therapy.

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The Left Shifted Oxyhemoglobin Curve in Sepsis:

A Preventable Defect

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Nine patients with severe sepsis were studied to determine causes for any alterations in oxygen dissociation. Seven of the patients had oxyhemoglobin curves shifted to the left of expected and diminished DPG levels. These deficiences were not corrected in one case. The other eight patients survived or expired with normal to elevated P_{50T} and DPG levels. In this study, three factors occurring either individually, in concordance, or in sequence were present when P_{50T} was decreased. Correction of these deficiencies lead to normalization and, in one case, exceedingly high P_{50T} and DPG levels. Where hypophosphatemia, acidosis, and transfusion of DPG deficient blood were avoided, no such change occurred. Hypophosphatemia is a common occurrence in the seriously ill patient whether or not hyperalimentation is used and may occur in spite of phosphate supplementation. Blood transfusions with CPD as the preservative are effective in reducing the severity of this disorder by the addition of an inorganic phosphate load. Septic shock itself had no untoward effect on oxygen dissociation. This held true even in the terminal stages of the disease process.

THE AMOUNT OF OXYGEN consumed by the body equals the cardiac output multiplied by the difference in oxygen content between arterial and venous blood. Oxygen content of blood is determined largely by the amount of oxygen in combination with hemoglobin. The equilibrium of the reaction may be viewed as being determined by substrate availability (that is, oxygen tension in the plasma environment and hemoglobin concentration) and the "kinetics" of the reaction (position of the oxyhemoglobin curve). Because the curve is sigmoidal, percent hemoglobin saturation and oxygen content are essentially maximal at oxygen tensions of 75 mm Hg or above. Once this plateau is reached, increases in PO_2 and shifts in the position of the oxyhemoglobin curve have little effect on oxygen content. Venous blood normally has a PO_2 of 40 to 45 mm/Hg. This range falls on the "steep" or vertical portion of the oxyhemoglobin curve. Small changes in the position of the curve can cause large alterations in venous oxygen content at or below these partial pressures.

The organic phosphate 2,3-diphosphoglycerate (DPG) affects the position of the oxyhemoglobin curve (also designated as P_{50T} when measured at standard condition) by decreasing the affinity of hemoglobin for oxygen. Reports,[8,19,20] reviews,[14,22] and textbooks[18] have recently suggested that intraerythrocytic DPG deficiency is an integral part of the pathophysiology of sepsis and septic shock. It is the purpose of this paper to analyze the changes in oxygen dissociation observed in such states.

Materials and Methods

Nine patients with severe sepsis were studied. All of the group had high fever, tachycardia, tachypnea, leuko-

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cytosis, and potentially overwhelming infections. Six of the nine had one or more episodes of hypotension characterized by attending physicians as septic shock. Pathogenic organisms were cultured from the blood in five of the nine cases.

In addition to the usual clinical parameters, the following were determined: DPG (by a modification of Lowrey's Technique[15]), arterial pH, oxygen and carbon dioxide tension,* plus serum phosphate and hemoglobin levels.† The position of the oxyhemoglobin curve at standard conditions (P_{50_T}) was measured by tonometering blood in known concentrations of carbon dioxide and oxygen at 37C. Percent oxyhemoglobin saturation at three different oxygen tensions was determined by spectrophotometer.† The pH of each sample was measured and a P_{50_T} was established utilizing computer programs derived from the Severinghous nomogram and the Hill Equation.[24]

Results

Six of the nine patients died. Infection was established as the major contributor to the demise of the five who had postmortem examinations. Three patients survived. These three patients had no definite episodes of septic shock, but manifested the other signs of severe sepsis. While seven of the nine patients had diminished P_{50_T} and DPG levels during a portion of their septic course, only one of the patients who expired had such defects at time of death.

Three conditions were found to be associated with depressed P_{50_T} and DPG levels; recent massive infusion of old blood, acidosis and hypophosphatemia. In some instances two or more were present at the same time or as part of the train of debilitating events in the course of a patient's illness. With the correction of these deficiencies, the position of the P_{50_T} returned to normal or supernormal levels and there was a concomitant rise in DPG levels. Table 1 summarizes the patients' profiles.

Massive Transfusion of Old Blood

Three patients had massive transfusions. Acid-citrate-dextrose (ACD) was the blood preservative utilized during the early part of one of the patient's illness. After her admission to Peter Bent Brigham Hospital, the blood preservative was citrate-phosphate-dextrose (CPD), as was true with all other patients.

Case Reports

Patient 1, D.M.: This 14-year-old white female was admitted to another hospital. She underwent emergency subtotal colectomy for ulcerative colitis. Infection of the right abdominal wall was noted three days later. At that time, rectal bleeding necessitated an abdominal perineal resection. She continued to bleed from her incisions and multiple transfusions of ACD blood were given. She was transferred to Peter Bent Brigham Hospital two weeks after

TABLE 1. *Profiles of Septic Patients*

Patient	Age	Primary Diagnosis	Associated Conditions	Complications	Cause of Death	Decrease in pH	Decrease in PO_4	Decrease in DPG	Decrease in P_{50}	Significant Infusion of Stored Blood
D. M.	14	Ulcerative colitis	None	Clostridial wound infection	Clostridia	No	Yes	Yes	Yes	Yes
J. M.	19	Ulcerative colitis	None	Bilateral subdiaphragmatic abscesses	Survived	Yes	Yes	Yes	Yes	Yes
K. R.	75	Incarcerated hernia	Emphysema	Clostridial wound infection	Clostridial sepsis	Yes	No	Yes	Yes	No
T. H.	76	Prostatism	Bleeding stress ulcer	Septicemia, pancreatic and subdiaphragmatic abscesses	Survived	No	No	No	No	No
F. J.	15	Septic abortion	None	Infected hydrothroax renal failure	Sepsis	Yes	Yes	Yes	Yes	No
T. M.	76	Cerebellar tumor	Myocardial infarction	Perforated viscus	Peritonitis*	No	No	No	No	No
L. C.	29	Granulomatous colitis	Multiple small bowel fistulae	Intra-abdominal abscesses	Survived	No	Yes	Yes	Yes	No
E. C.	77	Ruptured aortic aneurysm	Severe coronary arteriosclerosis	Acute renal failure	Sepsis	No	Yes	Yes	Yes	No
J. Mc.	37	Gunshot wound to abdomen	None	Renal failure peritonitis	Sepsis	No	No	Yes	Yes	Yes

Normal pH was greater than 7.37. Normal PO_4 was 3–4.5 mg%. Hypophosphatemia was considered significant only if levels less than 2.7 mg% persisted for greater than three days. Normal DPG was 13 ± 1 μm/gm Hb. Normal P_{50} was 24.5 ± 3mm Hg.
* Clinical diagnosis. No postmortem examination performed.

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* Radiometer Acid-Base Analyzer PHM 71 Radiometer A/S Copenhagen, Denmark.

† I.L. 182 Co-oximeter, Instrumentation Laboratories, Lexington, Mass.

her original operation. Admission pulse was 130 and BP was 80/60. The patient, obviously jaundiced, was bleeding from open abdominal and perineal wounds. No evidence of disseminated intravascular coagulation was found. Gram negative rods were discovered on smears of aspirates from the abdominal wall. With the use of hyperbaria, antibiotics and infusion of whole blood, the patient improved transiently. An exploratory laparotomy performed during a hyperbaric treatment revealed widespread pelvic and retroperitoneal inflammation. Four days after admission, massive pleural effusions necessitated the placement of bilateral tube thoracostomies. Blood cultures grew out multiple organisms including *Clostridium perfringens* and *Escherichia coli.* In spite of continuing infusions of fresh blood and fluids, the patient deteriorated further, developing high output renal failure, respiratory failure, and a small bowel fistula. She expired a month after admission. During the last two week period, multiple blood cultures grew out *Escherichia coli.* At postmortem examination, the patient had the additional findings of hepatic vein thrombosis and bilateral acute tubular necrosis.

Comment

This patient had recurrent episodes of septic shock and bacteremia. Prior to her transfer to Peter Bent Brigham Hospital, she received massive quantities of ACD blood stored longer than 14 days. On admission she also received two units of CPD blood of greater than 14 days' age. At this time she was hypophosphatemic and had depressed P_{50_T} and DPG levels. Both the ACD and CPD blood were of such age that the intra-erythrocytic organic phosphates had been depleted. The patient was no longer hypophosphatemic after receiving CPD blood and was able to regenerate organic phosphates. With the use of fresh blood thereafter, normal DPG and P_{50_T} levels were maintained to the time of the patient's death. Figure 1 illustrates the pertinent findings.

Patient 2, J.M.: This 19-year-old white male was admitted to another hospital after having diarrhea for five days. Six days later, a caecal perforation with pelvic abscess was treated by tube caecostomy and drainage. A fecal fistula developed through the operative wound on the sixth postoperative day. Subtotal colectomy and "oversewing" of jejunal and ileal fistulae were performed. Tissue diagnosis was ulcerative colitis. The patient was transferred to Peter Bent Brigham Hospital two weeks later. At admission pulse was 120; BP, 128/70; respiration, 30; and temperature, 100F. A culture from a jugular catheter tip grew out *Staphylococcus aureus.* Colistin and carbenicillin were given. Four days later, perirectal and bilateral subdiaphragmatic abscesses were drained. Multiple cultures of the fistulae, abscess cavities, urine and sputum grew out *Escherichia coli* and *Pseudomonas aeruginosa* over the next month. Throughout these four weeks his temperature remained between 100 and 104F, while the heart rate was consistently 120–160 beats/minute. Blood pressure varied between 110/70 and 140/90. White cell count ranged from 5,500 to 21,000. The patient had recurrent toxic hallucinations. Multiple transfusions, large quantities of intravenous fluid, and protein hydrolysate hyperalimentation (Aminosol-Abbott Laboratories, Needham Heights, Massachusetts) were given during the course of his illness. The patient gradually improved and was discharged four months after admission with a mucocutaneous rectal stump fistula and a well functioning ileostomy. Phosphate, pH, DPG, hemoglobin and P_{50_T} changes during this period are shown in Fig. 2.

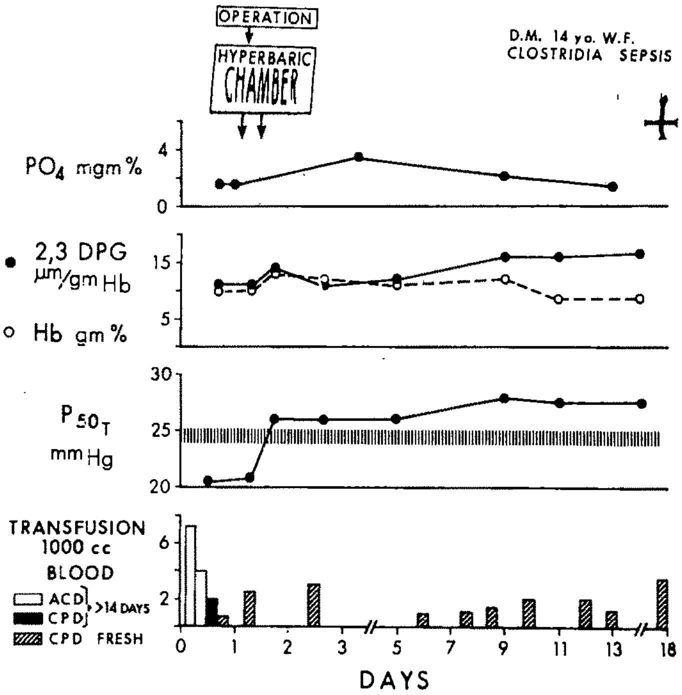

FIG. 1. The normal range (mean ± 2 standard deviations) of P_{50_T} in this and all other figures is shown by the bar with vertical stripes. pH in this patient was a constant 7.49 to 7.51 until the day of her death.

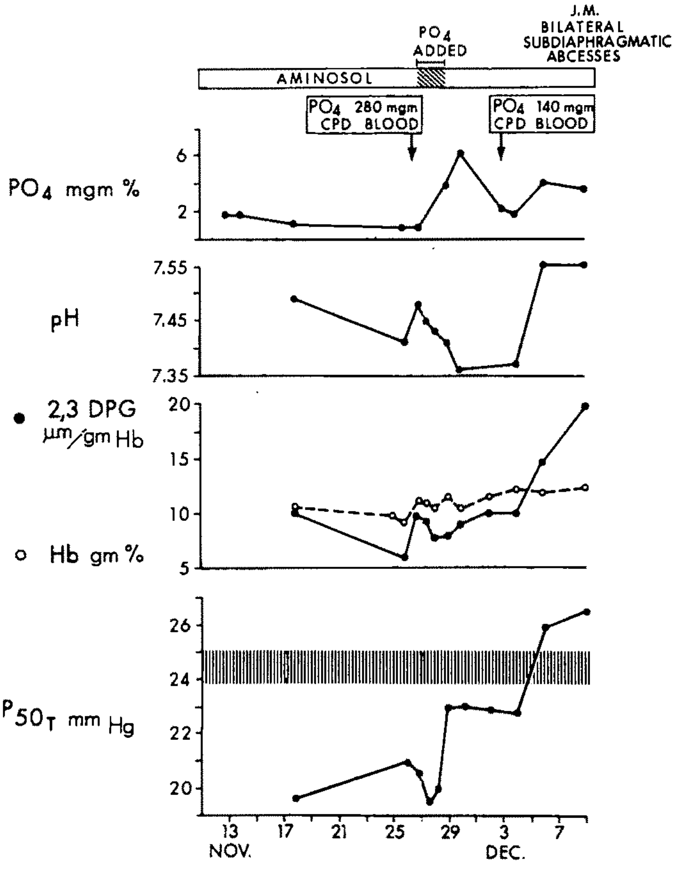

FIG. 2. Patient 2: Phosphate, pH, DPG, hemoglobin and P_{50_T} changes.

Comment

This patient had prolonged severe sepsis. The decreased P_{50_T} was originally the result of phosphate deficiency after hyperalimentation with solutions containing no phosphate. Infusion of 400 cc of DPG deficient, CPD stored red cells in this 40 kg, immobilized, anemic patient represented at least a 25% dilution of his red cell mass. Thus, P_{50_T} and DPG levels fell initially. Only after the serum phosphate rose, (because of the addition of inorganic phosphate contained in CPD blood), P_{50_T} and DPG levels could increase. With continued hyperalimentation, phosphate levels fell again, and the same effects of CPD blood were noted with the second transfusion. The second transfusion consisted of three units of packed red cells, with the total inorganic phosphate infused per unit amounting to only ⅓ of that in a unit of blood. The lack of further elevation of P_{50_T} during the period between transfusions was probably due to the mild acidosis present. For the remainder of his course, phosphate was added to the hyperalimentation solution. Figure 2 depicts these changes.

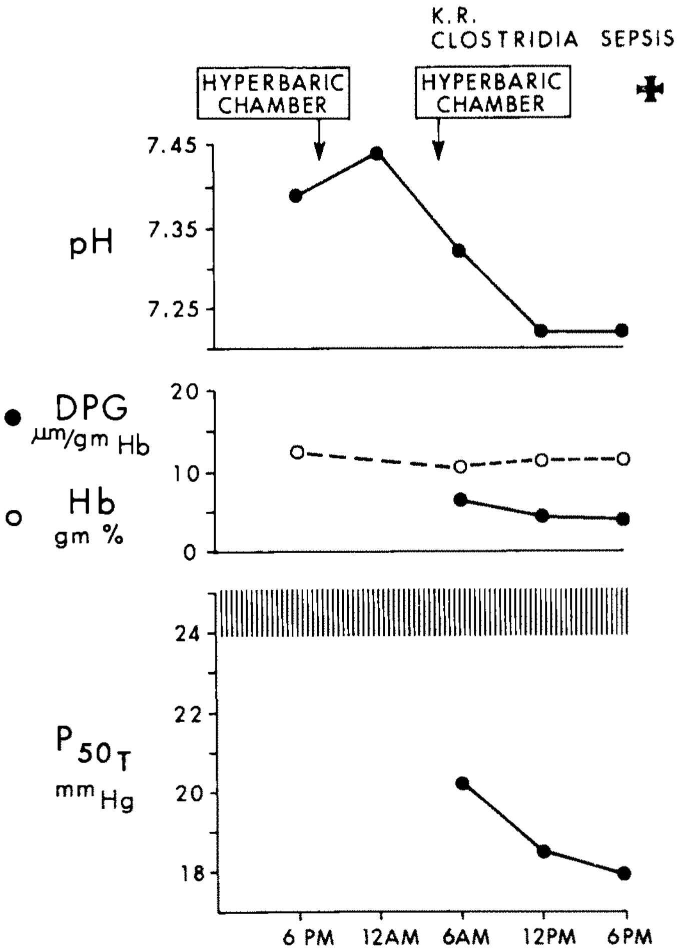

FIG. 3. Admission serum phosphate level was 3.6 mg% in this patient. No phosphate level was obtained the next day.

Acidosis

Three patients had respiratory or metabolic acidosis associated with a decreased P_{50_T}. Two of the three patients had evidence of both septic shock and bacteremia. In one case, correction of the acidosis and associated phosphate deficiency resulted in increased DPG and P_{50_T} levels. The patient survived. In the second instance the defects were corrected, but the patient expired. The third case represented acidosis without hypophosphatemia.

Case Report

Patient 3. K.R., a 65-year-old white male, was admitted to another hospital with abdominal pain. At laparotomy an incarcerated, non-stangulated inguinal hernia was found and reduced. Three days later the patient developed fever, hematuria and icterus. He was transferred to Peter Bent Brigham Hospital. On admission, pulse was 120; blood pressure 70/40; respiration, 16; temperature, 102F. The patient was icteric, agitated, and restless. Brawny edema was present over much of the trunk; crepitus was noted around the abdominal and groin incisions. The patient also had right lower lobe pneumonia. He was started on cephalothin and tetracycline intravenously, plus blood and plasma infusions. Hyperbaric therapy was begun. The next day, in spite of continuing massive infusions of plasma and isuprel and further hyperbaric treatment, his blood pressure continued to drop. He expired at 7:00 p.m. Cultures of tissue aspirates grew out *Clostridium perfringens* and blood cultures grew out diphtheroids. Postmortem examination confirmed the clinical impression of massive *Clostridium perfringens* infection. The pertinent findings in this case are shown in Fig. 3.

Comment

This patient had decreased P_{50_T} and DPG levels when first studied. As acidosis increased, both deficiencies became more prominent. No abnormalities of serum phosphate were noted.

Below a pH of 7.35, DPG production is inhibited progressively as hydrogen ion concentration rises. The depressed DPG levels seen were probably a result of acidosis and not any specific effect of sepsis. It can be overcome by coexisting hyperphosphatemia.[1] This patient was the only one in the series who died with P_{50_T} depression.

Hypophosphatemia

During septic periods, five patients had hypophosphatemia associated with abnormalities of DPG and P_{50_T}. Two of these patients were receiving intravenous hyperalimentation solutions containing no phosphate. When hypophosphatemia was obviated (with an additional correction of acidosis in one case) P_{50_T} and DPG levels were normalized or increased. One patient had hypophosphatemia and a depressed P_{50_T} without obvious cause when first studied. She was not on hyperalimentation or phosphate binders. One patient was treated with hemodialysis and aluminum hydroxide gel by mouth concomitantly. He also developed hypophosphatemia while not on hyperalimentation.

Case Reports

Patient 4. E.C., a 76-year-old white male, with a history of previous myocordial infarction, entered another hospital with a one day history of back pain and weakness. After emergency resection of a ruptured abdominal aortic aneurysm, the patient developed acute renal failure. On the first postoperative day, he had bloody diarrhea. Emergency laparotomy revealed no evidence of intestine with compromised viability. A tracheostomy was performed because of recurrent atelectasis. He was transferred to Peter Bent Brigham Hospital two days later. On admission pulse was 72; blood pressure, 160/80; and temperature, 98F. The patient was alert, cooperative, and had slight peripheral cyanosis. BUN was 98; white blood count was 7,200. He was placed on hemodialysis and aluminum hydroxide by mouth. An atrial flutter with a slow ventricular rate required the insertion of a demand pacemaker. His temperatures ranged between 102 and 105F. Multiple sputum and urine cultures grew out *Pseudomonas aeruginosa,* Bacteroides species and *Klebsiella pneumonia.* Kanamycin was given intermittently to maintain adequate blood levels. Massive infusion of blood and plasma substitutes were required to combat the recurrent episodes of hypotension occurring during the remainder of the patient's course. Hyperalimentation with protein hydrolysate (Amigen-Travenol Laboratories, Edison, New Jersey) was begun one month after admission. Aluminum hydroxide was stopped shortly thereafter. Ten days later, an isuprel infusion was required to maintain blood pressure, and blood cultures grew out Pseudomonas aeruginosa. The patient had a transient cardiac arrest after two more days and expired a few hours later.

Three dye dilution cardiac outputs were performed during the patient's hospital course. His heart rate was between 100 and 110 during the time the cardiac outputs were performed, with no evidence of hypovolemia or hypotension. The flow recorded was never above 3.5 liters per minute. At postmortem examination, the lower lobe of the right lung had multiple microabscesses. Acute pericholangitis, centrilobular hepatic necrosis, acute tubular necrosis, two old myocardial infarctions, and a severely compromised coronary circulation were also found. The parathyroid glands were normal. Figure 4. depicts the pertinent changes.

Comment

This patient died after recurrent episodes of septic shock and bacteremia. He was anemic and could not elevate cardiac output because of myocardial disease. In either instance both DPG and P_{50_T} levels usually are elevated well above normal. Hypophosphatemia prevented this compensation. The original phosphate deficiency probably was induced by the combination of "phosphate binders" by mouth and dialysis. After correction of the initial defect, the patient was maintained on hemodialysis and a hyperalimentation regimen which included phosphate. Hypophosphatemia did not occur. Multiple transfusions of CPD blood were given. Although unknown factors may also have prevented hypophosphatemia, the number of CPD transfusions helped maintain inorganic phosphate levels. As hyperphosphatemia occurred, DPG and P_{50_T} levels continue to rise. The terminal P_{50_T} and DPG levels were the highest ever recorded in this laboratory.

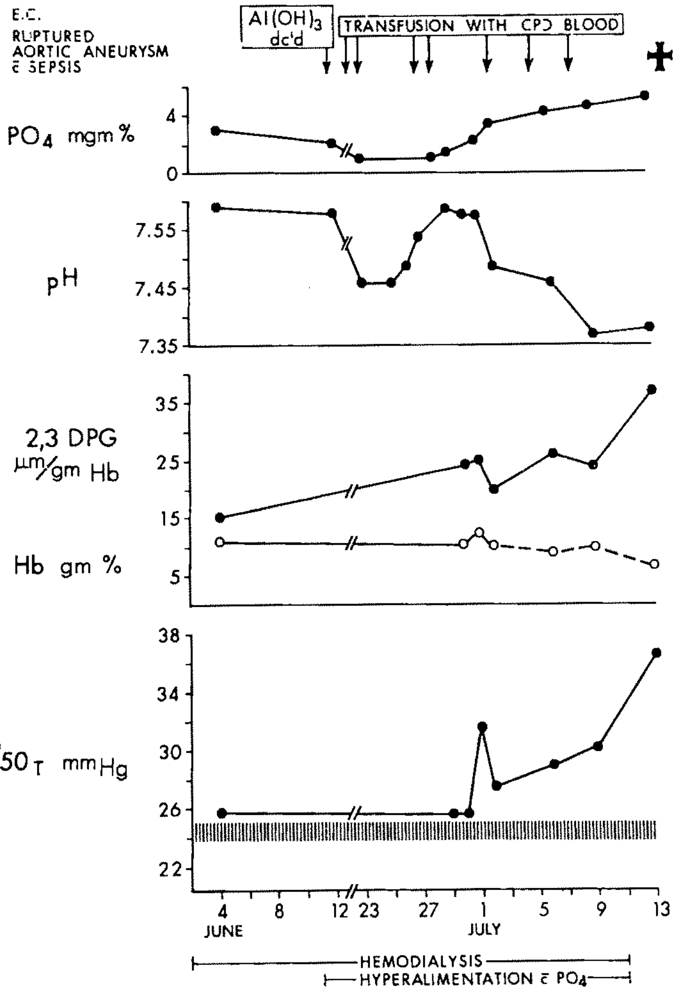

Fig. 4. Patient 4.

Patient 5. F.J., a 15-year-old white female, was transferred from a pediatrics hospital. Past history was unremarkable. One week prior to admission she attempted an abortion using a "sterile catheter." Two days later she developed chills, fever, vaginal bleeding, and hypotension. Admitting diagnosis was septic shock secondary to septic abortion. She was treated with penicillin, steroids, digitalis, and plasma expanders. She was transferred to Peter Bent Brigham Hospital five days after her original admission. At admission, pulse was 170; BP, 150/70; temperature 96.5F. A grade II/IV systolic murmur, no bowel sounds, and a large amount of vaginal debris were positive physical findings. White cell count was 12,100, SGOT was 63, and LDH was 432. Cephalothin and kanamycin were given. Dilatation and curettage was performed. She developed increasing fever, anemia, respiratory insufficiency, renal failure and hypertension. Blood cultures grew out Bacteroides species. Antibiotic therapy was changed to chloramphenicol, but she continued to have bacteremia with hypotension. Hemodialysis, steroids, digitoxin and hyperalimentation with Amigen were added to the regimen. Blood cultures began to grow out *Proteus vulgaris* two weeks later. Transient cardiac arrest occurred on this date. The patient expired 24 hours

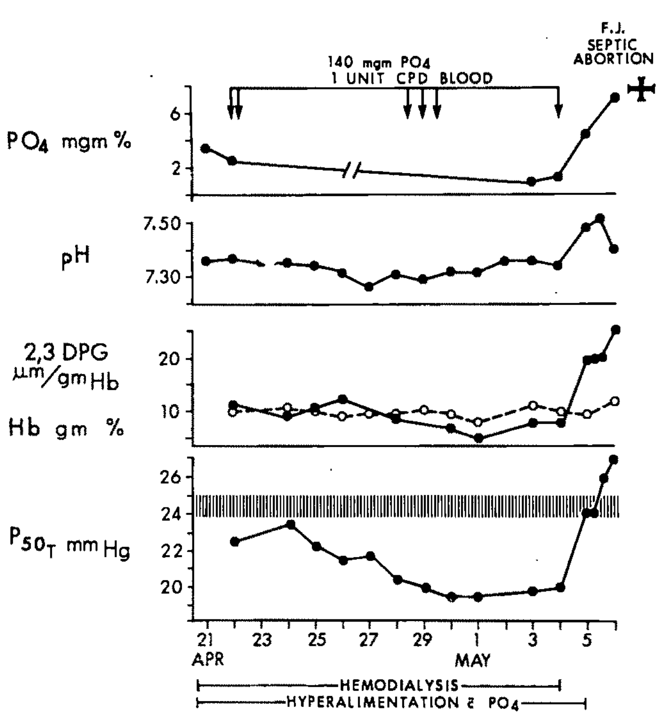

Fig. 5.

later. At postmortem examination bilateral necrotizing bronchiopneumonia with pulmonary abscess and empyema formation was found, as well as hepatic infarction and hepatic vein thrombosis. Pertinent findings are shown in Fig. 5.

Comment

This patient had repeated episodes of septic shock with multiple organisms being cultured from her blood. Her DPG and P_{50_T} depletion was primarily due to hypophosphatemia and to a lesser extent, mild acidosis. The phosphate deficiency existed in spite of hyperalimentation with standard amounts of phosphate and multiple blood transfusions of CPD blood containing 140 mgm of phosphate per unit of blood. The combination of increased phosphate use in metabolic pathways plus hemodialysis, a procedure which lowers serum phosphate levels, probably accounts for the electrolyte abnormalities. After cardiac arrest, hyperalimentation was stopped. Initially, the patient developed metabolic alkalosis and mild hyperphosphatemia. P_{50_T} and DPG levels rapidly rose. Later, pH dropped to 7.40, but serum phosphate rose to 6.0 mgm%. The continued increase in P_{50_T} during the final stages was due to hyperphosphatemia.

No Abnormalities

Two patients had no abnormalities of serum phosphate, P_{50_T}, or DPG. One died and one recovered. Neither massive transfusions of blood nor acidosis occurred during these patient's courses.

Discussion

Besides organic phosphate levels,[3,7] and the Bohr effect,[5] there are other modifiers of hemoglobin affinity for oxygen.[2,12,28] The importance of these factors needs further clarification. In acute alkalosis, P_{50} is lowered *in vivo*. Oxygen delivery is kept constant by a decrease in mixed venous oxygen tension.[28] The same mechanism obtains in moderate anemia (6.5 to 10 gms% of Hb),[29] in cases of myocardial dysfunction[30] and, acutely, after large losses of intravascular volume.[16] In states of hypoxia[13] and increased energy demands,[9] decreased venous oxygen tension plays a significant role in maintenance of oxygen delivery. DPG deficiency appears to be offset by this same mechanism of increased extraction.[6] Three major causes of DPG deficiency known to occur *in vivo* are hypophosphatemia,[23] acidosis,[1] and transfusion of large quantities of stored blood.[27] As a preservative for blood,[26] ACD has been the subject of increasing criticism. DPG and ATP levels are markedly reduced by the fifth day of storage. When CPD is used as a preservative, organic phosphates do not deteriorate until the seventh to tenth day.[4]

Another benefit of CPD preserved blood was apparent in the patients with hypophosphatemia. The effective inorganic phosphate in a unit of ACD preserved blood is that originally contained by the blood; approximately 20 mgm. While plasma inorganic phosphate levels in stored blood rise with length of storage, the phosphate increase is that produced by the degradation of organic phosphates. An equivalent amount of inorganic phosphate must be used to replete intracellular organic phosphates after transfusion of such blood. The inorganic phosphate in CPD preservative adds 140 mgm to body stores whenever a unit of CPD blood is infused. The normal 70 kg male has a total body water of 39,000 cc.[21] While one unit of ACD blood will have no effect on total body phosphate, one unit of CPD blood would theoretically increase inorganic phosphate concentration by approximately 0.4 mgm%. If total body water were of lesser magnitude, the increase would be more pronounced.

While the direct effect of acidosis *in vivo* offsets to a great degree the P_{50} changes due to inhibition of DPG, a sudden shift to alkalosis in such a situation would produce a double deficit in oxygen transport. The depression of P_{50} by alkalosis is additive with the depression due to decreased DPG. Patients with acute respiratory insufficiency often exhibit such changes of pH during treatment. Acidotic patients who suffer cardiac arrest often become acutely alkalotic due to hyperpnea and sodium bicarbonate infusion.

Alkalosis, under normal circumstances, rapidly depresses P_{50} *in vivo*, but more slowly stimulates DPG synthesis, elevating P_{50_T} in both adaptation to altitude[17] and to anemia,[29] maintaining the dissociation of oxygen at near constant levels *in vivo*. This paradoxical occurrence probably maintains homeostasis by an increase in enzymatic activity, thus increasing DPG synthesis. In acidosis the same paradox holds true, but in an opposite direction (acidosis inhibits DPG production, decreasing P_{50T} while acidosis itself has a direct effect of increasing P_{50} *in vivo*).

If phosphate deficiency occurs with alkalosis, the DPG changes and Bohr effects become additive because DPG cannot be produced. A much worse situation occurs than in isolated acute alkolosis where DPG values may be normal. On the contrary, where acidosis and hyperphosphatemia co-exist, the P_{50} *in vivo* may actually be far to the right of the P_{50T}

The roles of acidosis and old blood were not surprising. The high rate of occurrence of hypophosphatemia was not anticipated. The hypophosphatemia occurred in four situations: a regimen of hyperalimentation without phosphate; hyperalimentation and hemodialysis; hemodialysis and use of phosphate binders; a case in which none of these were present.

A discussion of the many causes of hypophosphatemia is beyond the scope of this paper. However, on one ward randomly picked for study, 35% of the patients were hypophosphatemic at some time during hospitalization. While it is not suggested that all these patients had DPG and P_{50T} depressions, we are in an era in which determination of inorganic phosphate levels must become as routine as other laboratory tests. Especially in the critically ill patient receiving hyperalimentation therapy, we can no longer depend upon small amounts of phosphate being infused and occasional serum phosphate levels determined as has been the standard.[10]

Relatively minor changes in venous oxygen tension can ordinarily offset the P_{50T} changes.[28] But at some point cardiac output must also increase.[21] The venous oxygen tension reserve is compromised already when anemia, hypovolemia or increased energy demands are present either singularly or in combination. Where compensation cannot be further made, lactic acidosis appears.[11] The small changes are best described by noting that a 2 mm shift in the oxyhemoglobin curve position or a 2 mm change in venous oxygen-tension at the normal value of mixed venous blood are equivalent to 1.12 liters of cardiac output change.[29]

In the individual with severe sepsis or septic shock, the additional insult of a shift in P_{50T}, although these shifts are small in quantity, must be met by relatively large increases in cardiac output once the venous oxygen tension reaches a critical level. The subsequent acidosis occurring when both mechanisms are exhausted will cause decreased oxygen affinity, temporarily offsetting the untoward P_{50T} changes *in vivo*. However, such acidosis could set off a cascading effect of further inhibition of DPG production with continued *in vivo* lowering of the P_{50} causing still further increases of lactic acid production.

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Benign Breast lesions: Punctate Calcifications

"All that glisters is not gold"—Shakespeare. Which should remind the uninitiated that one cannot depend upon the *roentgen characteristics of breast calcifications alone* to diagnose or exclude malignant breast disease. Witness the following, all proved benign breast lesions considered "cancer" by mammography.

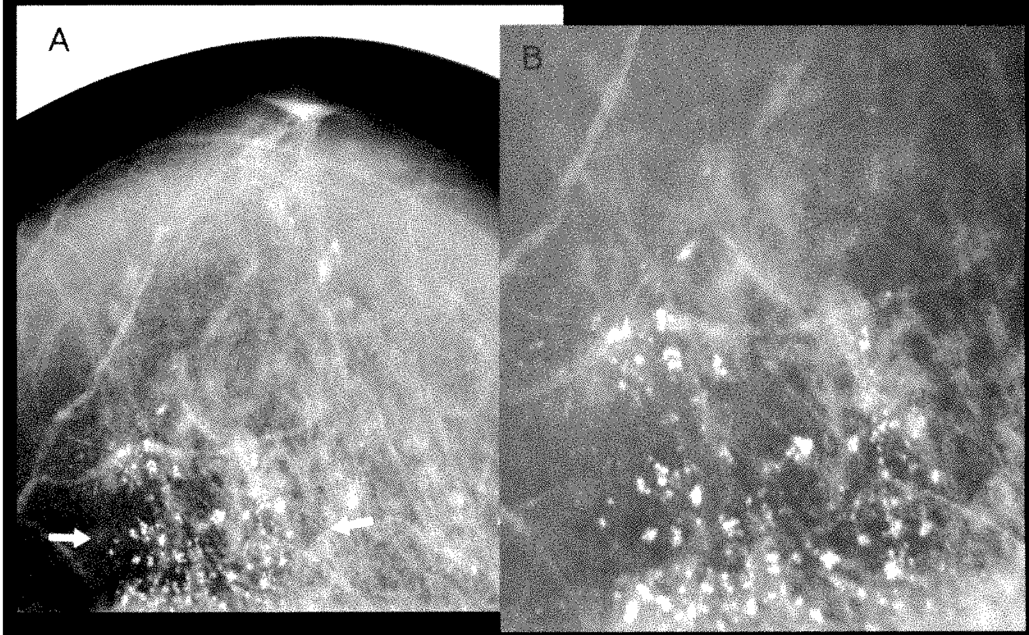
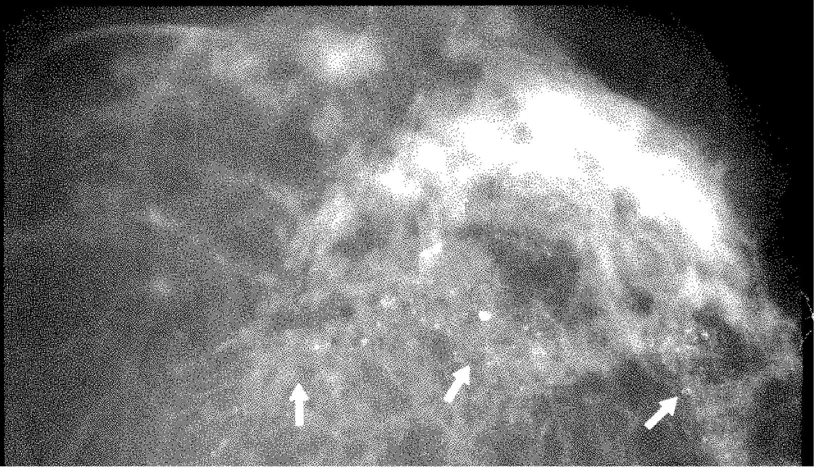


Figure I—Ductal Papillomatosis
A. Craniocaudal view reveals calcifications of varying size and configuration (arrows), seen to better advantage in Figure B, which look very much like the calcification seen in breast cancer. Clinically, the patient had no complaints. The breast was operated upon because of the mammographic suggestion of possible intraductal carcinoma. Biopsy revealed fibrocystic disease with proliferative changes including papillomatosis and adenosis.



ure II—
rocystic Disease
s breast, too, was removed
gically because of innu-
rable punctate calcifica-
ns (arrows) considered
ncer mammographically.
ast biopsy revealed dif-
e fibrocystic disease with
ifications in and around
ted ducts.

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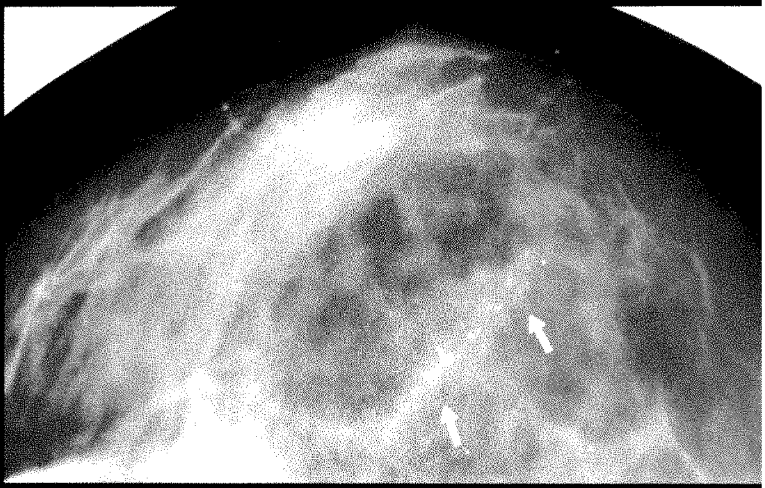
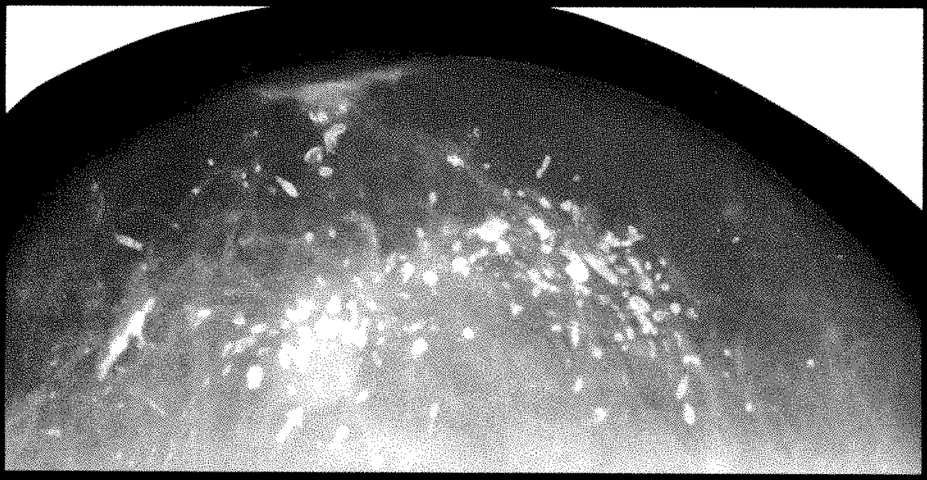


Figure III—
Fibrocystic Disease
Craniocaudal view reveals innumerable small punctate calcifications (arrows) irregular in size and outline, which suggested breast cancer by mammography. When biopsied, the patient proved to have localized fibrocystic disease with numerous foci of intraductal calcification.

Figure IV—Comedomastitis Plus Carcinoma
Craniocaudal view reveals innumerable coarse linear and somewhat round calcifications distributed throughout most of the breast. The patient was known to have a small palpable mass in the center of this breast. On close inspection, a modular density may be seen (arrow), which is partially obscured by the benign calcifications that surround it. The nodule proved to be a small (1.5 cm) carcinoma; the rest of the breast revealed extensive mammary duct ectasia with calcifications in the wall of the ducts. The experienced observer remembers that sclerosing adenosis, ductal papillomatosis, and fibrocystic disease may reveal tiny punctate calcifications that mimic cancer.



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Pulmonary Bacterial Susceptibility in the Burned Rat

DONALD P. DRESSLER, M.D., WILLIAM A. SKORNIK, M.S.

An *in vivo* model system, using the burned rat as a model of altered host resistance, was developed and studied to investigate the lung's ability to handle an aerosolized bacterial insult of either *P. aeruginosa* or *S. aureus*. Rates of lung bacterial clearance were correlated with mortality, bacteriologic and histologic results. Susceptibility of the lung to sepsis was shown to be directly related to host resistance and was significantly increased following cutaneous thermal injury. Exposure of burned, non-seeded rats to a bacterial aerosol on day one post burn resulted in a mortality of 50% *(P. aeruginosa)* and 11.1% *(S. aureus)*. This mortality clearly demonstrates an increased susceptibility at day one post burn. In contrast, this susceptibility gradually decreased with time; no mortality in the burned rat when exposed on day six post burn or in the normal, unburned rat. Histologic findings correlate well with the mortality results showing a gradually decreasing severity of pneumonitis if aerosol exposure was further delayed. Lung bacterial clearance studies revealed that the initial good response of the pulmonary defense mechanisms immediately following aerosol challenge are short-lived and that a marked increase in pulmonary bacterial susceptibility occurs as early as 24 hours following thermal injury.

From the Department of Surgery, Harvard Medical School, Cambridge Hospital and Youville Hospital, Cambridge, Massachusetts

RECENTLY, EXTENSIVE WORK has been carried out in our laboratory describing the relationship of the burn wound to the bacterial susceptibility of the lung.[1-3] These studies were initiated because of the emergence of pneumonitis as a major clinical problem similar to that found in other areas.[4] Respiratory tract infections in these patients are also most commonly due to organisms of low virulence, i.e. *Pseudomonas aeruginosa* or *Klebsiella-Aerobacter* and reflect an increased susceptibility rather than a new epidemic.

These studies, using the burned rat as a model of altered host resistance, have shown that susceptibility of the lung to sepsis is directly related to host resistance and specifically the ability of the lung to clear an aerosolized bacterial insult. By using a bacterial aerosol generated in specially designed, multi-purpose controlled atmosphere chamber, it was shown that the normal rat's lung is able to clear 98.10 ± 0.75% of *P. aeruginosa* organisms in four hours. This was determined by comparing the number of viable bacteria remaining in the lung (after four hours) with the number of viable bacteria immediately following removal of the animal from the chamber.

In the 20% body surface area third degree burned rat model, clearance is normal at four hours unless the burn wound is purposely seeded with *P. aeruginosa*. In the topically seeded, burned animals there was a marked decrease in the bacterial clearance to 16% at twenty-four hours post burn and after that time, the bacteria in the lung actually increases following exposure to the aerosol. Topically, mafenide acetate cream did not affect normal clearance in non-seeded animals. When utilized to control sepsis in the topically seeded groups, a reduction below 1×10^5 *P. aeruginosa* organisms per gram of eschar restored the lung's normal capacity to clear the bacterial insult.

Although these studies demonstrated that the presence of a lethal *Pseudomonas aeurginosa* burn wound sepsis rapidly resulted in a marked decrease in lung bacterial clearance, they did not parallel the clinical situation in which a patient dies from a pneumonitis while the burn wound has a level of bacteria that is otherwise compatible with survival. These studies also do not fully provide insight into the complex mechanisms that affect pulmonary bacterial susceptibility. It was the objective of

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this study to investigate the lung's ability to handle an aerosolized bacterial insult of both *P. aeruginosa* and *S. aureus* in animals with a percent of body surface area burn that would be expected to be compatible with survival, and to correlate these results with mortality, bacteriologic and histologic studies.

Method

Approximately 1000 male Sprague-Dawley rats weighing 180–200 gm, bred and raised in our own facility, were used in this study. They were fed standard (Purina) rat chow containing no antibiotics and given water *ad libitum*. The animals were maintained in individual cages in air-conditioned rooms.

The rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (40 mg/kg). The back was shaven with a number 40 blade electric clipper and the animal placed in a container designed to expose 50 cm^2 of the back, an area representing approximately 20% of the body surface area. The exposed back of each rat was then immersed in water kept at 98 C for exactly ten seconds. This resulted in a uniform, full-thickness burn. Rats that were to be topically infected were seeded 10 minutes after scalding by the application of one ml. of 18-hour trypticase soy broth culture containing approximately 1×10^8 organisms of *P. aeruginosa*.

Three separate groups of animals were evaluated to determine the effect on mortality, histology and the ability of the lung to clear an aerosol bacterial challenge.

Mortality

Separate groups of animals (25) representing each burn group were assigned to a mortality study in order to prevent a biased interpretation of results. Different groups of these animals were subjected to bacterial aerosol of either *P. aeruginosa* or *S. aureus* immediately following burning and 8, 24, 72 and 144 hours postburn. These animals were maintained in the laboratory for at least 21 days post experimentation. Rats that appeared moribund and within a few hours of death on the basis of difficult respiration, lack of coordination, difficult movement and failure to respond to stimulation, were considered non-survivors and thus were made available while still alive for histologic and bacteriologic studies. Changes in susceptibility were assessed by comparisons of the mortality rates.

Histology

In order to assess the effect of burning on the lung directly, histologic studies were performed on separate groups of animals from each of the *S. aureus* or *P. aeruginosa* aerosol. The entire respiratory system including trachea was removed *in toto* and fixed in 10% normal buffered formalin solution. The tissue was sectioned at six microns and stained with hematoxylin and eosin. Special stains, gram stain, Teplitz' modified Giemsa stains, were used to identify bacteria.

Lung Bacterial Clearance

The ability of the lung to clear a bacterial insult of *P. aeruginosa* and *S. aureus* was determined in each of the groups. Separate groups of animals were utilized for these studies. Determinations were made on days 1, 3, 6 and 10 postburn. Sixteen rats, four at a time, were placed in the exposure chamber for each run. The animals were place in individual wire mesh cages, small enough to prohibit any change in orientation, but large enough so that normal respiration is not restricted. After a 15-minute acclimation period, they were placed in the exposure chamber of a multi-purpose controlled atmosphere chamber designed and built in our laboratory. The apparatus consists of six parts: aerosol generator, mixing chamber, heating chamber, exposure chamber, filter system and control unit. The aerosol generator consists of a nebulizer and bacterial suspension reservoir. Air, activated by a solenoid valve in the control unit, flows into the nebulizer at four liters per minute. The outlet of the nebulizer was directed into the mixing chamber where the aerosol is diluted and dried by air flowing from a secondary source at 30 l/min. In the center of the mixing chamber, a circular metal disc was suspended to help remove large droplets and provide for more uniform mixing of bacteria in the air. Five minutes after the secondary flow was started, the nebulizer was activated. The exposure period lasted 30 minutes. It was predicted from previous data that approximately 1×10^9 organisms were suspended during this period and that $2.44 \pm 0.42 \times 10^5$ organisms were deposited in one gram of lung tissue. Immediately after a run, the exposure chamber was opened and the rats removed. The animals to be sacrificed immediately were given an intraperitoneal injection of sodium pentobarbitol (40 mg/kg) while those to be sacrificed four hours later were placed in individual standard cages in an air-conditioned room whose temperature and humidity are kept constant. The lungs, including all intrapulmonary bronchi, were removed aseptically and homogenized with trypticase soy broth in a Duall tissue grinder immersed in an ice bath. The homogenate was then serially diluted and replicate agar plates made. These were incubated at 37 C for 24 hours. Bacterial retention and thus clearance was determined by counting the numbers of viable bacteria in the lungs of rats sacrificed immediately and four hours post exposure.

Results

Mortality

The mortality rates of animals burned and/or burned and topically seeded with *P. aeruginosa* organisms and then exposed to *P. aeurginosa* or *S. aureus* aerosol are shown in Table 1.

TABLE 1. *Results of the Mortality Study when Burned Animals Are Exposed to Bacterial Aerosol*

Aerosol	Model	Aerosol 1-Day Postburn	Aerosol 3-Day Postburn	Aerosol 6-Day Postburn	Aerosol 10-Day Postburn
S. aureus	Burned	11.1%	0%	0%	0%
	Burned Seeded	100%	100%	100%	100%
P. aeruginosa	Burned	50%	18%	0%	0%
	Burned Seeded	100%	100%	91.6%	100%

When the normal rat is exposed to either an aerosol of *P. aeruginosa* or *S. aureus*, no deaths occur. The infliction of a 20% third degree scald results in *no* mortality unless the burn wound is topically seeded with *P. aeruginosa*, following which 100% mortality occurs. Exposure of the burned, non-seeded animal to a bacterial aerosol on day one postburn results in a mortality of 50% *(P. aeruginosa)* and 11.1% *(S. aureus)*. This mortality clearly demonstrates an increased susceptibility at day one postburn, in contrast to *no* mortality in the normal rat and in the burned rat when exposed day six postburn. As expected, some mortality does occur on day three postburn. Also, as might be expected, the animals exhibit a different susceptibility to each genus of bacterial aerosol.

Histology

When a group of normal animals is exposed to *P. aeruginosa* and sacrificed at 1, 3, 6, 10 and 21 days later, an infiltration of acute inflammatory cells occurs in the peribronchial wall, but no necrosis or destruction of the wall occurs (Fig. 1, 3 days postaerosol). A slight infiltration of acute inflammatory cells occurs in the interstitium, but this is local, and edema, congestion and cellularity are not prominent.

Similarly, when a group of normal animals was exposed to an aerosol of *S. aureus* and randomly sacrificed at regular intervals, histologic studies showed more prominent inflammatory changes as compared to those animals exposed to *P. aeruginosa*. There was a dissolution of bronchial epithelium with infiltration of acute inflammatory cells in the bronchial and peribronchial walls. Scattered focal pneumonitis occurred, with acute inflammatory cell infiltrates in the interstitium and congestion and deposition of fibrinous material on the alveolar wall. Focal necrosis and destruction of the bronchial wall was also present.

Animals burned and exposed to a *P. aeruginosa* aerosol on day 1 postburn show more marked changes as com-

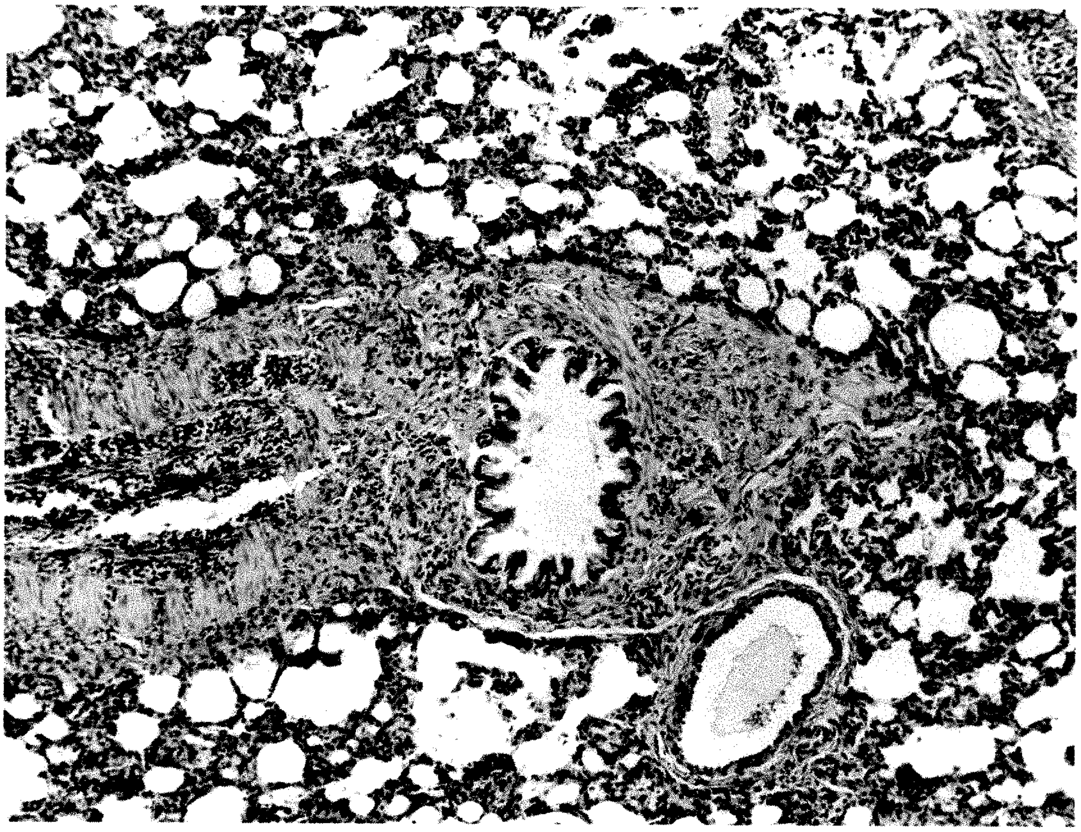

FIG. 1. Photomicrograph of the lung of a normal rat exposed to a *Pseudomonas aeruginosa* aerosol and sacrificed three days post exposure (×180).

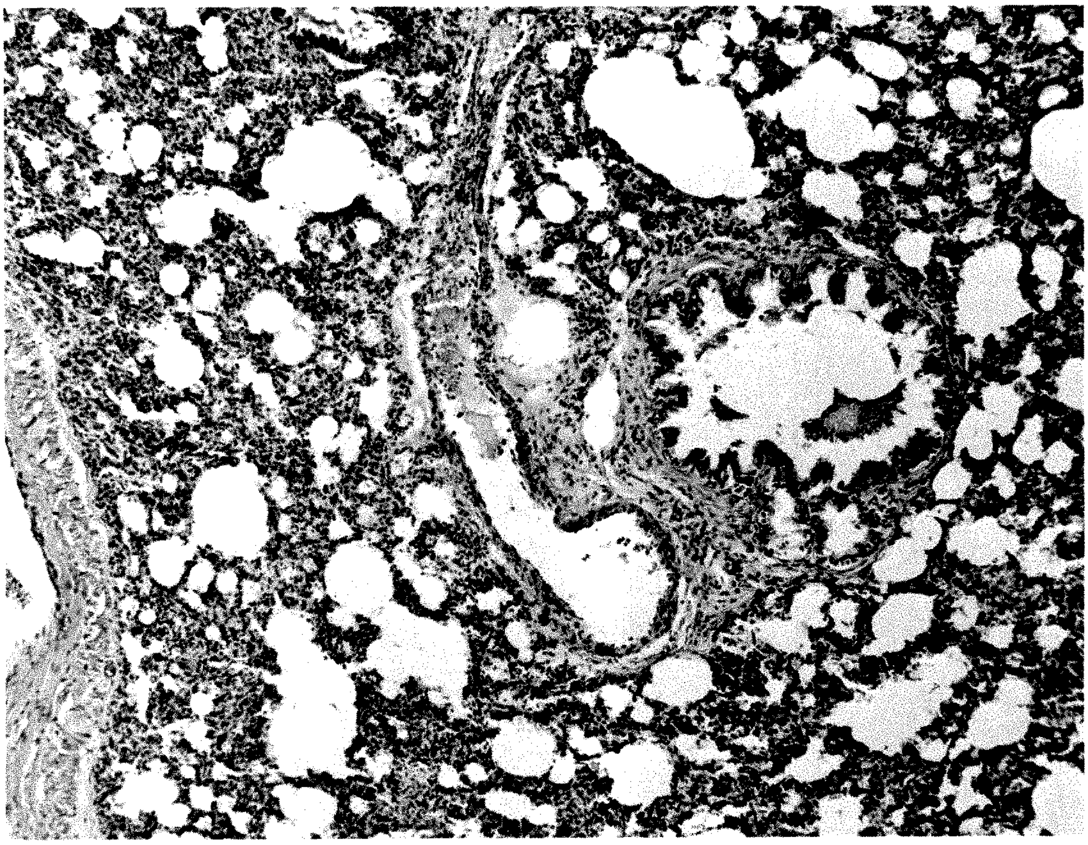

FIG. 2. Photomicrograph of the lung of a burned rat exposed to *Pseudomonas aeruginosa* aerosol one day postburn and sacrificed three days post aerosol (×180).

pared to the normal animal. By day 3 postaerosol (Fig. 2), the inflammatory changes have become confluent with less clearance of the inflammation with severe inflammatory cell infiltration of the interstitium and alveolar walls. By day 10 however, in those selected animals who survived, (see Table 1), there was a distinct improvement in most of the lung tissue with focal congestive destructive changes confined mainly to the peribronchial areas.

Similarly, when animals were exposed to an *S. aureus* aerosol one day following a 20% third degree scald, inflammatory changes reach their peak three days later with degenerative changes in the bronchial mucosa and severe involvement of the bronchial and peribronchial tissue. Again on the tenth day in those surviving animals there was resolving of the pneumonitis.

In comparison, when burned animals were exposed to *P. aeruginosa* on the sixth day postburn, or to *S. aureus*, (Fig. 3), there was distinctly less inflammatory reaction, infiltrations, and a more rapid clearing, and the bronchitis and pneumonitis resolve much earlier. Exposure of burned, seeded animals to a *P. aeruginosa* or *S. aureus* aerosol (Fig. 4) resulted in severe marked gross abscesses.

The actual ability of the animal to clear an aerosol bacterial insult on Days 1, 3, 6 and 10 postburn is shown in Fig. 5 *(P. aeruginosa)* and Fig. 6 *(S. aureus)*. While normal animals rapidly clear bacteria within 4 hours, and maintain this rate of clearance, animals exposed 1 day postburn to a *P. aeruginosa* aerosol clear only 49% of the inhaled organisms in four hours. By eight hours, they have cleared 97.7%, but the effect is short-lived. At 24 hours, there are only 16.1% fewer organisms in the lung than at the time of the initial bacterial challenge. This 24-hours finding is interesting, since 66% had an increased bacterial growth, while 34% showed an excellent clearance (Table 3). These results are reflected in mortality studies: 50% showing improvement in four hours, while the remaining 50% appeared to have had a lethal dose and went on to die. Exposure to bacterial insult on days 3, 6 and 10 resulted in an immediate response of varying degrees with a consistent decrease by 8 hours following exposure and complete clearance by 48 hours. Results of these studies show three stages: an initial bacterial clearing followed by increased bacterial multiplication, and then a secondary or delayed response. This suggested a two-phase mechanism for ridding the lungs of bacteria.

A similar depression in lung bacterial clearance was noted following exposure to *S. aureus* aerosol. While at one day, initial excellent clearance was not followed by a depression, the animals initially showed increased bacterial growth at both four and eight hours, and a depressed clearance at 24 hours. Exposure on days 3, 6 and

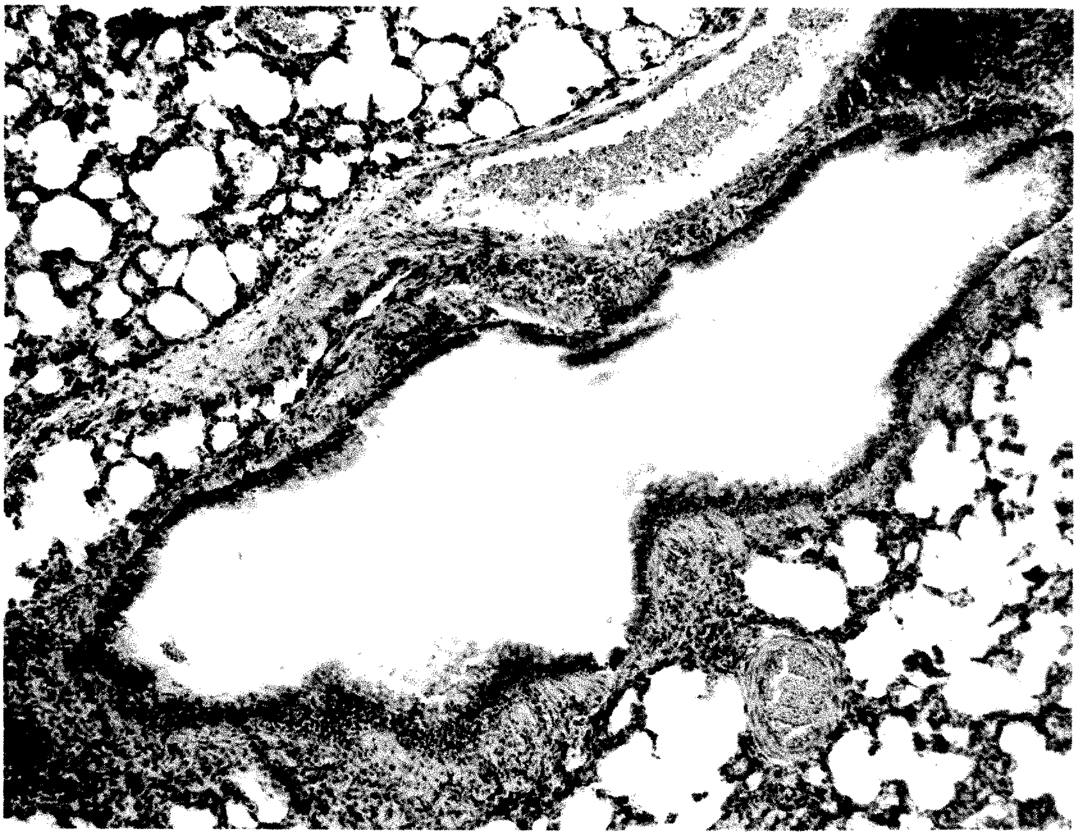

FIG. 3. Photomicrograph of the lung of a burned rat exposed to *Staphylococcus aureus* aerosol six days postburn and sacrificed ten days post aerosol (×180).

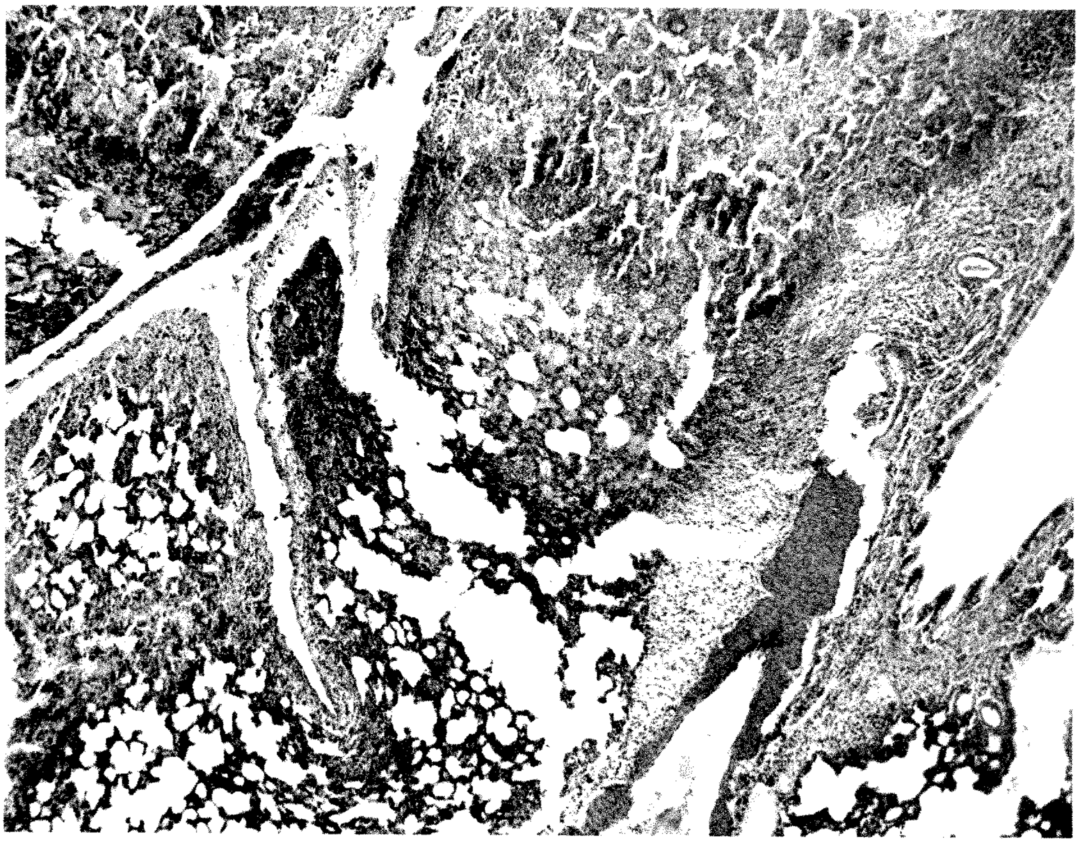

FIG. 4. Photomicrograph of the lung of a burned rat topically seeded with *Pseudomonas aeruginosa* organisms and exposed to a *Staphylococcus aureus* aerosol six days postburn and sacrificed three days postaerosol (×70).

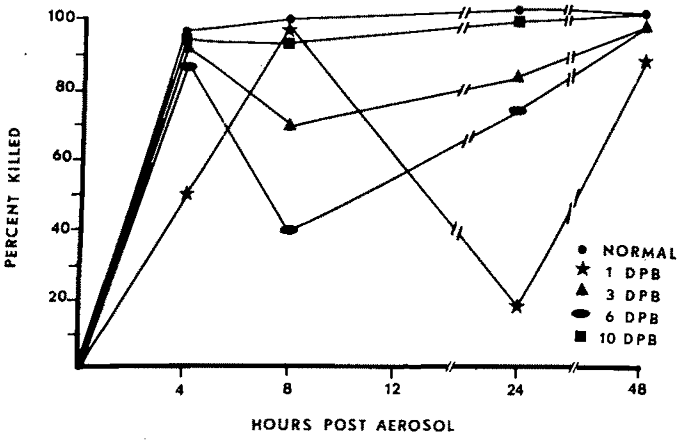

FIG. 5. Ability of the rat lung to clear a *Pseudomonas aeurginosa* aerosol on various days postburn.

TABLE 2. *Per Cent of Lung Bacterial Clearance (mean ± S.D.) at 4, 8, 24 and 48 hours Following Exposure to Pseudomonas aeruginosa or Staphylococcus aureus Aerosol on Days 1, 3, 6 and 10 Post Burn*

	4	8	24	48
		Pseudomonas aeruginosa		
Normal	93.8 ± 2.1	97.9 ± 1.3	98.8 ± 0.2	99.8 ± 0.1
1 DPB*	49.0 ± 15.7	97.7 ± 0.9	16.1 ± 5.2	87.2 ± 3.9
3 DPB	90.9 ± 2.8	67.4 ± 10.3	81.2 ± 5.9	98.6 ± 0.2
6 DPB	84.7 ± 4.1	37.8 ± 15.5	72.1 ± 6.8	98.5 ± 0.3
10 DPB	94.5 ± 1.3	91.8 ± 3.8	99.8 ± 0.1	99.2 ± 0.1
		Staphylococcus aureus		
Normal	79.2 ± 5.5	83.2 ± 4.2	97.9 ± 1.9	99.6 ± 0.1
1 DPB	45.1 ± 10.2	37.8 ± 7.4	77.8 ± 4.9	91.6 ± 2.1
3 DPB	71.2 ± 7.3	47.8 ± 8.2	82.2 ± 3.1	93.5 ± 1.3
6 DPB	73.6 ± 6.1	49.4 ± 9.7	87.9 ± 2.5	96.3 ± 0.9
10 DPB	76.1 ± 6.5	64.4 ± 9.1	89.7 ± 2.8	98.0 ± 0.4

* Days Post Burn.

10 demonstrated a gradual return to normal, although the standard error of individual clearance groups (Table 2) is of interest.

The real significance of a decreased percent of lung bacterial clearance is shown in a distribution table (Table 3). This table demonstrates that when the average clearance of a group is 76% or better, 93.6% of the animals fall into this group, and 6.4% clear more than 50%. When the average lung bacterial clearance is between 51% and 75%, only 48.4% of the animals in the group fall into the excellent level (above 75%), 28.1% into the good (51–75% average lung bacterial clearance), 9.7% clear an average of 25–50%, 3.9% of the individual animals clear 0–25% and 9.9% do not clear at all, but show increased growth. When the group average percent of lung bacterial clearance falls between 25% and 50%, 21.2% have excellent clearance, another 21.2% have good clearance, 15.2% have only fair clearance, and 6.1% have poor clearance while 36.3% show positive growth. When the average percent of lung bacterial clearance falls below 25%, 66.6% show positive growth, while interestingly 33.4% show good or excellent clearance.

Comment

The mortality rate postburn and post aerosol challenge coupled with the histologic findings clearly establish the validity of the model, while demonstrating the marked increase in pulmonary bacterial susceptibility immediately following a cutaneous thermal injury.

Mortality studies demonstrate an increased susceptibility to pulmonary sepsis immediately following cutaneous thermal injury, with an increased susceptibility to Pseudomonas compared to Staph. This susceptibility gradually decreased with time unless wound sepsis developed. Histologic findings correlate well with the mortality results showing a gradually decreasing severity of pneumonitis if aerosol exposure was further delayed. In those animals topically seeded with *Pseudomonas aerugi-*

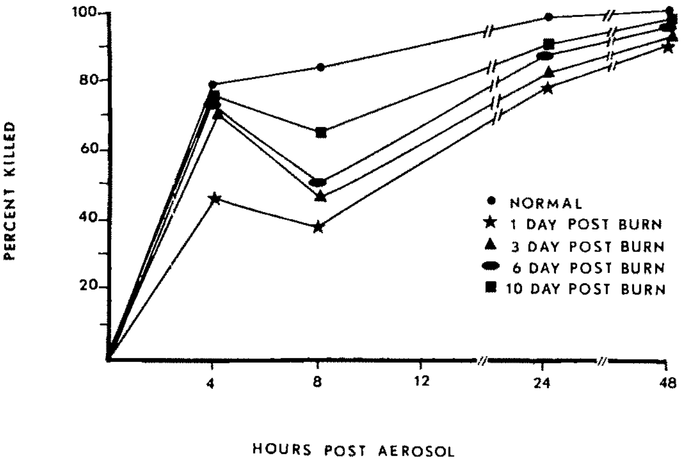

FIG. 6. Ability of the rat lung to clear a *Staphylococcus aureus* aerosol on various days postburn.

TABLE 3. *Distribution of per cent of Lung Bacterial Clearance of Individual Animals in Comparison to the Average Lung Bacterial Clearance of Each Experimental Group*

Individual Animal Clearance Within Each Group	Average % Lung Bacterial Clearance of the Various Groups 1–25	26–50	51–75	76–100
Excellent (76–100%)	2*	14	50	88
Good (51–75%)	2	14	29	6
Fair (26–50%)		10	10	
Poor (1–25%)		4	4	
Increased Growth	8	24	10	

* Number of animals.

nosa, it was interesting that although there is 100% mortality, pneumonitis is not found unless the animals receive an aerosol challenge, in which case the resultant infection is markedly severe and would in itself be lethal even without continued burn wound sepsis.

The lung bacterial clearance studies also provide important *in vivo* data concerning the mechanism whereby the lung handles an aerosol challenge. The initial good response of the pulmonary defense mechanisms immediately following challenge and previously cited, decreases at 24 hours, demonstrating a marked increase in pulmonary bacterial susceptibility following thermal injury.

Analysis of the distribution table is particularly significant in that it identifies at each clearance level two basic groups: those that are able to clear bacteria and presumably will continue to clear and survive, and those where the host defense mechanisms have failed. This latter group, which shows increased bacterial growth, will go on to develop a fatal pneumonitis if left untreated. The reason why some animals are able to respond and other are not warrants further investigation. However, bacterial clearance followed by depression and then increased clearance does provide some insight into underlying mechanisms by suggesting a two-phase mechanism. During the first phase, local host defense mechanisms already actively present are capable of a good response but secondarily, replenishment is required after 24 hours for ultimate survival.

These studies also suggest that the burn depresses or delays the secondary or replenishment phase but does not affect the initial response.

Since the alveolar macrophage has been demonstrated to be the primary factor in lung bacterial clearance, several possible modes of action are suggested: 1) decreased production of promonocytes in the bone marrow, the accepted precursor of the alveolar macrophage, 2) blocked release into the blood stream similar to that described as the mode of action of several corticosteroids, 3) adversely altered distribution of the circulating monocytes; 4) decreased chemotaxis (directly or indirectly) and decreased migration of monocytes to the alveoli; 5) decreased activation of the alveolar macrophage 6) or secondly through decreased complement or antibodies, both specific and nonspecific.

Although this secondary depressed response is also present with exposure to a *S. aureus* challenge, it is evident that the response to *Staph* is different from that to *Pseudomonas.*

There appears to be a delay or depression in the initial response to *S. aureus* aerosol induced by the cutaneous injury, but thereafter the lung and also the animal, as evidenced by the lowered mortality rate compared to *P. aeruginosa,* handles the challenge well.

Further investigation concerning the mechanisms of lung bacterial clearance and particularly the role of the alveolar macrophage might serve to clarify these various responses to thermal injury.

The parallel between these studies and the clinical situation is obvious: At a time when susceptibility is highest, during the first 24 hours postoperatively, endotracheal suction, contamination of the anesthetic circuit, etc. can provide continuous contamination of the respiratory tree. At this stage, depending on the level to which susceptibility has been altered, even a seemingly minimal inoculation could be fatal.

While it might appear that improved aseptic techniques are the solution and certainly should be strived for, it is equally obvious that no technique can be developed whereby one bacterium will not be present. Frequently, the patient himself is the source, as is the case with emphysema and chronic bronchitis where the bacteria growing within the alveoli can assume a pathogenic role should the opportunity arise.

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Pancreatic Secretion in Response to Jejunal Feeding of Elemental Diet

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The instillation of elemental diet into the proximal jejunum of dogs results in a brisk pancreatic secretory response, but the fluid is watery and "enzyme-poor." The administration of the caloric equivalent in a standard blenderized ward diet induces pancreatic enzyme secretion. Although elemental diet does not "rest" the pancreas, the failure of these preparations to stimulate pancreatic enzyme secretion gives them a theoretical advantage as a nutritional source in the convalescent phase of acute pancreatitis.

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PATIENTS CONVALESCING from severe pancreatitis often present problems with prolonged gastric retention and consequent nutritional deprivation. The "triple-tube" technique of managing these complications, with gastrostomy, jejunostomy, and cholecystostomy is often employed when severe pancreatitis is encountered at laparotomy.[3] The method provides for long term gastric decompression, without a levine tube, and a safe route for nutritional support.

The instillation of food into the proximal jejunum has been regarded by many clinicians as being relatively free of hazard, insofar as pancreatic stimulation and the reactivation of a smouldering pancreatitis is concerned. It is known however, that when jejunum is exposed to various nutrients, pancreatic secretion results.[2]

It has recently been claimed that elemental diets do not elicit pancreatic secretion, and that these formulas should be used in the nutritional management of pancreatitis. No data recording the volume and type of pancreatic secretion resulting from elemental diet feeding, either orally or by jejunostomy, are currently available. A study was therefore designed in dogs to determine the effect on pancreatic secretion of elemental and blenderized diets, infused through a jejunostomy.

Methods

Four adult dogs were prepared with Thomas cannulae in the stomach, duodenum and proximal jejunum. The main pancreatic duct was cannulated and the catheter allowed to lie in the duodenum. When the animals were fully recovered from the laparotomy (usually three weeks) the experiments were commenced.

In each animal, a stable 50% of maximum pancreatic secretory response was first obtained by infusing secretin 3 μ/Kg and pancreozymin CCK 6 μ/Kg. These 50% maximal doses were ascertained by constructing a dose response curve for each animal prior to testing.

The pancreatic secretory response to the jejunal feeding of elemental diet (Table 1) and the nutritional equivalent of blenderized ward diet (Table 2) was then measured. Elemental diet has been extensively tested in human volunteers and no toxic effect has been shown by a spectrum of hepatic, renal, and haematological determinations. Two experiments with elemental diet infusion, and two with blenderized diet were carried out on each animal. (Eight elemental diet infusions and eight blenderized diet infusions).

In each experiment, the duodenostomy and gastric cannulae were opened. The stomach was allowed to drain freely. The pancreatic cannula was removed from

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TABLE 1. *Elemental Diet Composition*

	Grams/ 1000 Cal		Caloric Contribution/ 1000 Cal	
Protein Equivalent	24.07		96	
Protein Hydrolysate Powder		22.94		92
Added Amino Acids		1.13		4
Fat	34.29		304	
Soy Oil (Lightly Hydrogenated)		26.63		240
MCT (75% C_8–25% C_{10})		6.66		55
Lecithin		1.00		9
Carbohydrate	149.93		600	
Corn Syrup Solids		63.20		253
Sucrose		77.34		309
Tapioca Starch		9.39		38
Total	233		1000	
pH 5.80				

the duodenum and a basal secretory rate determined over one hour. The plateau of 50% maximal secretion was first established. Jejunal feeding with either elemental or blenderized diet was then given by infusion through the jejunostomy cannula. Test infusions were made through a catheter inserted well down the jejunum in order to avoid reflux into the duodenum. No reflux was noted at the duodenal cannula. Elemental diet feedings were prepared with 50 gm of diet in 200 cc of water, while the blenderized ward diet consisted of a low residue preparation with the same caloric value (1 calorie/cc). The diet infusion was completed over one hour. Fifteen-minute collections of pancreatic secretion throughout the basal, infusion and post infusion period were analysed for HCO_3 and protein (enzyme) concentration.

Results

Jejunostomy feeding with elemental or blenderized diets did not "rest" the pancreas, and clearly had no inhibitory effect. Elemental diet in the jejunum increased the volume and HCO_3 content of pancreatic secretion (p .001 and .05) above the 50% of maximum plateau. (Figs. 1 and 2 and Table 3).

When compared to blenderized diets, elemental diet infusion resulted in a greater volume (p .007) and increased HCO_3 content of pancreatic secretion. The protein (enzyme) concentration in pancreatic juice fell when elemental diet was infused (p .0001).

Blenderized diets, however, increased the protein content of pancreatic juice above the plateau (p .05). The opposite effects of blenderized and elemental diet on pancreatic enzyme secretion is shown in Fig. 3.

The results are summarized in Table 3, and the contrasting effects of elemental and a blenderized ward diet on volume, protein and HCO_3 concentration are shown in Figs. 1–3.

Discussion

The infusion of nutrients through a feeding jejunostomy is not without risk in patients with subsiding pancreatitis. It has been recognized for many years that pancreatic secretion is stimulated by the presence of various

TABLE 2. *Blenderized Tube Feeding*

	Grams	Protein	Fat	Carbohydrate
Fruit: Unsweetened Orange Juice	50	0.5	0	5.5
Vit. Apple Juice	150	Tr	0	18.0
Sweetened, strained	200	0.8	0.9	32.2
Egg: Pasteurized whole	150	19.5	18.0	0
Cereal: Pre-cooked infant, dry, "mixed"	50	7.5	1.5	34.7
Corn Syrup	40	0	0	30.0
Bread: Enriched white, crustless	100	8.0	4.0	52.0
Margarine: Fortified	20	0	16.0	0
Cream 9%	120	4.0	11.0	5.5
Whole Milk	720	24.0	24.0	36.0
Skim Milk Powder	48	17.2	0.4	24.8
Lean Meat or Poultry: Strained	240	30.7	19.4	0.5
Vegetables: "All" vegetables, strained	100	1.7	0.5	8.5
Non-starchy vegetables, etc.	200	2.8	0.8	12.6
Potatoes: Dehydrated flakes, dry	50	3.6	0.3	42.0
Vegetable Oil	30	0	30.0	0
Prepared Dessert: Salt free custard	120	6.0	6.0	14.0
Water to bring volume (ml.) to:	3,000			
Totals		126.3	132.8	316.3
Calories:		2,965		
pH		6.25		

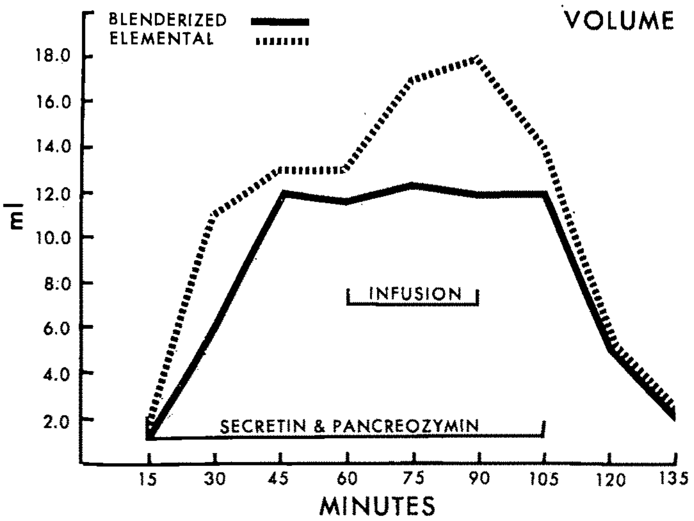

Fig. 1.

Figs. 1–3. The effect of blenderized diet and elemental diet on the volume (Fig. 1), HCO_3 (Fig. 2) and protein concentration (Fig. 3) is compared in the same animal tested on subsequent days. Blenderized diet induces a prompt increase in protein (enzyme) concentration of the pancreatic juice, but no change in HCO_3 concentration or volume/15 minute interval. Elemental diet however, causes a further increase in volume, and a sharp drop in enzyme concentration.

food products in isolated jejunal segments. Although a feeding jejunostomy provides a convenient means of supplying calories and protein in patients with gastric retention, it is sometimes forgotten that a mechanism for pancreatic secretion is still intact, even though the gastroduodenal mucosa is by-passed.

Theoretically, intravenous feeding would not stimulate pancreatic secretion, although there is no data available as yet to confirm this. Complications associated with placement of catheters, and the relatively limited calorie and protein intakes possible, make the intravenous route less desirable.

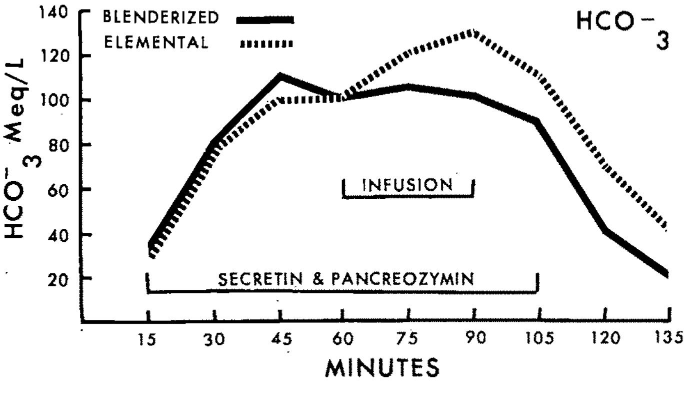

Fig. 2.

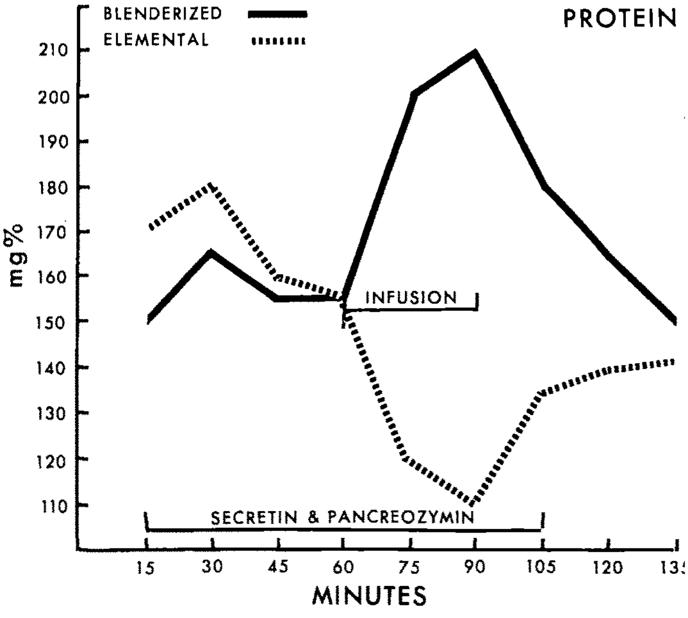

Fig. 3.

Clearly, a jejunal feeding which supplied a high calorie, high protein intake without stimulating pancreatic secretion would be highly desirable, and such claims have been made for elemental diets (Flexical). Brown reported that dogs fed the elemental diet orally for ten days had elevated trypsinogen levels in pancreatic tissue, and that secretory granules remained in a resting state.[1] This group further reported on patients managed with the elemental diet and made frequent reference to the "pancreatic rest" induced by elemental diet feeding.[4]

Direct measurement of pancreatic secretion does not support this concept. Instilling elemental diet into the jejunum induces a brisk pancreatic response. It may be important however, that the elemental diet appears to induce a secretin-like pancreatic response (high volume, HCO_3 rich, enzyme poor). The caloric equivalent in a blenderized diet results in pancreatic enzyme secretion (panocreozymin effect). These findings support the histochemical and electromicroscopic data of Brown, which appears to demonstrate a resting pancreas, from the standopint of enzyme secretion.

Whether the patient with a subsiding pancreatitis is fed orally, or by jejunostomy feeding, there would appear to be a clear theoretical advantage in the use of an elemental diet. The best route for administration of the diet is by feeding jejunostomy, and surgeons finding severe pancreatitis at laparotomy, or performing major pancreaticoduodenal surgery, should anticipate gastroduodenal obstruction, ileus, fistulas, pseudocysts and abscesses and provide a jejunostomy for nutritional support.

TABLE 3. *Pancreatic Secretion in Response to Elemental and Blenderized Diet*

	Mean Basal Output/15			Mean Plateau Output/15			Mean Feeding Output/15			Mean Post Feeding Output/15		
	Vol ml	HCO_3 MEq/L	Protein mg%	Vol.	HCO_3	Protein	Vol.	HCO_3	Protein	Vol.	HCO_3	Protein
Elemental Diet												
Dog #101	1.2	30	170	9.8	95	133	12.2	130.0	113.5	3.5	47.5	149.5
				12.3	100	182.5	18.0	139.0	139.0			
Dog #102	1.6	47	156	8.4	125	160.0	15.3	110	109	3.5	50	156.0
				13.9	100	157.5	17.5	122.5	115			
Dog #103	1.2	45	132.5	9.1	98	129	15.2	116.0	98.0	3.25	57.5	142.5
				12.6	129	129	17.2	120.0	97.0			
Dog #104	2.0	42.5	125	10.0	90	130	15	120.0	100	3.0	40	137
Mean	1.5	41.1	146.0	10.8	110.5	145.5	15.9	122.0	108.7	3.42	45.0	146.2
Blenderized Diet												
Dog #101	1.1	37	147.5	11.9	105	155	12.1	100.6	205.0	3.5	45	157.75
				9.5	99	150	10.1	85.0	207.5			
Dog #102	1.6	58	150	10.9	130	137.5	11.2	138	188.7	3.5	60	153
				9.9	115	136.5	9.8	122	188.0			
Dog #103	1.5	49	105	8.4	100	120	9.4	114	180.9	3.0	55	119.75
				8.1	103.3	117.5	9.4	114	170.0			
Dog #104	1.7	40	130	10	100	135	11	110	170	3.0	40	135
Mean	1.5	46	133.1	9.7	104.6	136.0	9.0	111.9	188.4	3.22	49.0	114.0
Elemental Diet	1.5	41.1	146.0	10.8	110.5	145.5	15.9	122	108.7	3.42	45.0	146.2
Blenderized Diet	1.5	46	133.1	9.7	104.6	136.0	9.0	111.9	188.4	3.22	49.0	114.0
							P = .007		P = .0001			

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Mechanism Responsible for the Cardiovascular Depressant Effect of Protamine Sulfate

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The mechanism of protamine-induced hypotension and bradycardia was investigated in anesthetized, heparinized dogs. Several groups of animals with intact circulation were studied for their responses to protamine under control conditions and following the administration of various pharmacological agents. The parameters observed include femoral arterial pressure (FAP), central venous pressure (CVP), left ventricular pressure (LVP) and its rate of rise (dp/dt), left ventricular contractile element velocity of shortening (Vce), maximal Vce (V max) and cardiac output (CO). Various groups were studied under the following pharmacological conditions: autonomic cholinergic blockade by atropine; alpha and beta adrenergic receptor blockade using phenoxybenzamine and propranolol respectively; ganglionic and adrenal medullary block using hexamethonium, and depletion of endogenous histamine by means of compound 48/80. Another group was placed on total cardiopulmonary bypass thus isolating the heart from the peripheral circulation. The effect of protamine on the vascular tree alone was then observed by monitoring FAP before and after protamine administration. The findings indicate that the cardiovascular effects of protamine are produced by a direct effect on the myocardium and vascular tree.

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THE USE OF EXTRACORPOREAL CIRCULATION has necessitated the administration of heparin. At the termination of cardiopulmonary bypass, protamine sulfate is used to neutralize the anticoagulant effect of heparin.[5] Unfortunately, the use of protamine is commonly followed by hypotension and bradycardia[1,6] which can be detrimental to patients with a marginal cardiovascular state. The mechanism underlying these untoward side effects to protamine administration was investigated in animals with intact circulation and with cardiopulmonary bypass. Our findings and conclusions are the subject of this report.

Materials and Methods

Forty adult mongrel dogs weighing 15–26 kg were anesthetized with intravenous thiopental sodium, intubated and ventilated with a Harvard mechanical respirator.

Animals with Intact Circulation

Thirty-six dogs were studied in this group. The heart was approached through a trans-sternal incision, extending into the left fifth and right fourth interspaces. Polyethylene catheters were introduced into the left femoral artery, left femoral vein and left ventricular cavity to measure the central venous pressure (CVP), femoral arterial pressure (FAP), left ventricular pressure (LVP) and its rate of rise (dp/dt). Left ventricular contractile element velocity (V_{ce}) was determined from isovolumic pressure (IP) and dp/dt; maximal V_{ce} (V max) by construction of IP to V_{ce} curve and extrapolation to zero load.[8] Cardiac output (CO) was determined by an electromagnetic flow probe (Statham) placed around the ascending aorta. Electrocardiographic tracings were ob-

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tained in every case. All data were recorded on a Sanborn multichannel recorder using Statham transducers.

Animals were subdivided into 6 groups (A to F) with 6 dogs in each group. Every animal received intravenous heparin 5 mg/kg followed by protamine sulfate, 10 mg/kg. In group A, both carotid arteries were exposed in the neck. The integrity of the carotid sinus reflex after heparin-protamine administration was tested by bilateral clamping of the carotid arteries proximal to the sinus region. Groups B to F were pretreated with the following drugs administered intravenously: Group B) hexamethonium chloride, 10 mg/kg, in order to block the autonomic ganglia and to prevent epinephrine release by the adrenal medulla; Group C) atropine sulface 0.5 mg/kg to block the postganglionic parasympathetic receptors (vagal block). After 10 minutes, parasympathetic block was tested by administering 2 μg/kg of norepinephrine. Norepinephrine administration is normally followed by rise in the blood pressure and reflex bradycardia, however, in a fully atropinized animal the rise in blood pressure will occur while the reflex vagal bradycardia will be abolished. Group D) also received phenoxybenzamine (Dibenzyline) 5 mg/kg with a waiting period of 30 minutes to achieve the required sympathetic alpha receptor blockade; Group E) propranolol (Inderal) 1 mg/kg with a 10-minute waiting period allowed to induce block of sympathetic beta receptors; Group F compound 48/80 (a condensation product of p-methoxyphenethyl methylamine with formaldehyde) 0.1 mg/kg slowly over a period of 20 minutes to deplete endogenous histamine.[10,11]

A sample of blood was withdrawn from one animal in each group before and after the administration of heparin-protamine and analyzed for its pH.

Animals with Extracorporeal Circulation

Four dogs (Group G) were placed on total cardiopulmonary bypass by appropriate cannulation. The heart was then isolated by clamping the ascending aorta and pulmonary artery. The effect of protamine on the vascular tree was then assessed by injecting the drug into the arterial inflow of the extracorporeal pump at a dose of 10 mg/kg. FAP before and after protamine administration was recorded.

Results

Results are summarized in Table 1. In Group A, which received no premedication, heparin, protamine administration led to an appreciable reduction of all the indices measured: a mean drop of 39% in mean FAP, 44% in IP, 38% in dp/dt, 31% in V max and 33% in CO. The reduced values were noted in every animal and were statistically significant. In all 6 dogs, simultaneous bilateral clamping of the carotid arteries proximal to the carotid sinus promptly reversed the hypotensive bradycardic effect of protamine. However, on removing the clamps, hypotension and bradycardia recurred.

Pretreatment with hexamethionum in Group B, atropine in Group C, phenoxybenzamine in Group D, propranolol in Group E and compound 48/80 in Group F did not abolish or reverse the effects noted in Group A control animals. The mean decreases in each group presented in Table 1 are consistent, reproducible and significantly different from zero. The small differences among the mean percentage decreases in the six groups for FAP were not clinically important although they just met statistical significance at the 5% level. (One way

TABLE 1. *Mean Percentage Change of Various Indices Following Heparin/Protamine Administration in Groups A to G*

	Group A	Group B	Group C	Group D	Group E	Group F	Group G
Premedication	None	Hexamethonium	Atropine	. . henoxybenzamine	Propranolol	Compound 48/80	Extra Corporeal Circulation
Mean FAP (mm Hg)	−39	−24	−29	−29	−31	−25	−24
CO (ml/min)	−33	−26	−29	−28	−32	−32	—
IP (mm Hg)	−44	−33	−42	−38	−30	−41	—
dp/dt	−38	−32	−40	−36	−45	−41	—
V max (ML/sec)	−31	−27	−33	−27	−30	−27	—

Mean FAP: Mean femoral arterial pressure
CO: Cardiac output
IP: Isovolumic left ventricular pressure
dp/dt: Rate of rise of intraventricular pressure
V max: Maximal left ventricular contractile element velocity

analysis of variance applied to the logarithms). The differences among the mean percentage decreases in CO, IP, dp/dt, and V max were even smaller and not statistically significant.

In group G where the animals' vascular tree was isolated from the heart by total cardiopulmonary bypass and aorto-pulmonary cross-clamping, protamine injection still produced a reduction in mean femoral arterial pressure that averaged 24%, quite similar to the value obtained in the other groups.

No significant change in pH was noted after heparin-protamine administration.

Discussion

Protamine sulfate administration is known to cause hypotension and bradycardia,[1,6] yet the site and mode of action remains a subject of controversy and debate. The present series of experiments was designed to answer some of the questions raised. The clinical situation was simulated by administering protamine only after heparin has been given and in a dose of 2 to 1. Some authors have advocated a neurogenic reflex mechanism to explain the cardiovascular responses to protamine administration.[1,6,9] The validity of the concept was tested in Group A animals. In all of them, proximal carotid arterial clamping reversed the hypotension and bradycardia produced by protamine. This testifies to the integrity of the carotid sinus reflex which is mediated via the animal's autonomic pathways. To elucidate this further, different sites in the autonomic nervous system were blocked in various animal groups. Heparin-protamine was then administered to determine if any of these anatomically different blockades could modify the cardiovascular responses to the drug. Group B animals in which hexamethonium chloride in large dosage was used to block autonomic ganglia and the adrenal medulla, responded to protamine in a manner similar to that in dogs with intact ganglia (Group A). Femoral arterial pressure, maximal left ventricular contractile element velocity and cardiac output all were again substantially reduced. Therefore, we have concluded that protamine does not produce its cardiovascular effects by blocking the ganglia of the autonomic nervous system.

In Group C animals, the postganglionic parasympathetic receptors were protected from any possible reflex cholinergic action of protamine by adequate doses of atropine sulfate. However, as in Group A dogs, almost the same hypotensive response and myocardial contractility depression following protamine injection were obtained, providing evidence that a parasympathetic reflex mechanism is not involved. Similarly, possible action of the drug on sympathetic beta receptors was excluded by finding that Group D animals pretreated with blocking doses of phenoxybenzamine responded to protamine in a fashion similar to the preceding groups. Propranolol used in Group E dogs in doses sufficient to block the sympathetic beta receptors, also failed to avert the cardiovascular depression caused by protamine. The preceding findings, therefore, dispute the involvement of reflex neural phenomena or a blocking action upon adrenergic receptors in protamine-induced hypotension and bradycardia.

The possibility of sensitivity and histamine release due to protamine injection was raised by Shelley *et al.*[12] in experiments with rats and guinea pigs. Kern and Langer[7] failed to elicit sensitivity to the drug in guinea pigs after repeated intraperitoneal injections. However, in dogs, Jacques[6] showed that a histamine-free preparation of protamine still produced hypotension. In the present study, depletion of the animal's stores of histamine was accomplished in Group F by prior treatment with compound 48/80. Subsequent protamine administration was followed by the same effects documented in Group A dogs. This finding substantiates previous evidence of Jacques and Kern that histamine plays no significant role in this regard.

Goldman and his associates[2] demonstrated depression of myocardial contractility after protamine injection, however, Gourin *et al.*[3,4] disputed these findings and even suggested that the drug is inotropic to the myocardium of the dog. In our experiments the contractile state of the intact dog's heart was quantiated by estimating the maximal velocity of left ventricular contractile element shortening. The same experimental model advocated by Mason and associates was used and the maximal velocity was determined from the instantaneous relation of the rate of pressure rise and the pressure developed in the left ventricular cavity during isovolumic contraction. Invariably in Groups A to F, myocardial contractility substantially decreased after protamine administration.

Further proof of a direct effect of protamine on the vascular tree was obtained in the present study by the findings noted in Group G animals. They were put on total cardiopulmonary bypass and the ascending aorta and main pulmonary arteries were clamped. Protamine injection into the inflow limb of the extracorporeal circuit, that is to say, in the isolated but intact vascular tree, led to prompt, significant reduction of the femoral arterial pressure.

Additionally, no significant blood pH changes were noted after heparin-protamine and, therefore, pH variations are not involved.

The results of these experiments have led us to believe that the cardiovascular effects of protamine sulfate are brought about by a direct action of the drug on the animal's heart and vascular tree.

These findings were made use of in our patients undergoing protamine infusion to neutralize heparin at the conclusion of cardiopulmonary bypass. We found that the following measures are frequently successful in preventing hypotension: 1) Administration of inotropic agents particularly calcium chloride or calcium gluconate; isoproterenol or epinephrine if the patient has no serious tachycardia or arrhythmias. Norepinephrine is occasionally used as it does not cause tachycardia and effectively reverses the vasodilation produced by protamine. 2) If the patient's central venous and left atrial pressures permit, the rate of fluid administration is increased. This compensates for the increased capacity of the vascular system induced by protamine.

Acknowledgment

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Aspiration of Blood and Pulmonary Host Defense Mechanisms

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The effect of aspiration of blood on pulmonary host defenses was studied in the rat. Sham and experimental rats had 0.2 ml of saline or blood/100 g body weight injected into their tracheas. One or 24 hours after aspiration rats were challenged with aerosolized, radiolabeled (^{32}P), *S. aureus*. Fourteen hours after bacterial challenge, lungs were removed and intrapulmonary bacterial inactivation was quantified. Significant impairment of bacterial inactivation occurred at both 15 and 38 hours after aspiration of blood, but not after saline. The pulmonary consolidation after aspiration of blood was focal in nature. The lung weight increased but fractional water content decreased. Arterial pH, pCO_2 or pO_2 were unaffected by aspiration of blood. The number and viability of macrophages recovered by lavage were similar in control, sham and experimental groups. If similar impairment in pulmonary host defenses occurred in man following aspiration of blood, the patient with aspiration of blood would have an increased susceptibility to bacterial infection.

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BLOOD MAY BE ASPIRATED following maxillofacial injury[23] or hematemesis. In addition, blood may enter alveoli following intrapulmonary hemorrhage due to direct injury[6,8,23,24] or intrinsic lung lesions such as tuberculosis, bronchitis and neoplasia.[5,9] Since intraperitoneal blood contributes to the development of peritonitis[3,7,28] it is possible that the morphological reaction to aspirated blood or the blood itself may increase the likelihood of bacterial pneumonia.

The purpose of this study was to evaluate intrapulmonary bactericidal activity in the rat after intratracheal injection of blood. Since the alveolar morphological reaction to the blood may vary with time, the intrapulmonary bacterial challenge was given both one and 24 hours after intratracheal injection of blood. Changes in pulmonary bacterial inactivation were related to arterial blood gases and pH, lung water, pulmonary microscopic anatomy, and to the number of viable macrophages obtained by bronchial lavage since these factors may influence host responses to bacteria in the lung.[4,10,12,20,25]

Methods

Male Wistar rats* were divided into three groups with similar mean weights. The rats were lightly anesthetized with ether and their tracheas were surgically exposed. Sham and experimental rats had 0.2 ml of saline or blood per 100 g body weight injected through a 27 gauge needle

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* In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences—National Research Council.

into the trachea. In anesthetized control rats, the needle was introduced into the trachea but no fluid was injected. Blood for aspiration was obtained from a femoral vein of a second rat after the trachea of the experimental recipient was exposed. Less than 10 seconds elapsed between collection of blood from one rat and intratracheal injection of blood into the other. To prevent forceful expulsion of blood or saline from the trachea and lungs, the proximal trachea was compressed at the time of injection. The incisions were closed and rats were allowed to recover one or 24 hours before being challenged with bacteria.

Bacterial Challenge

At one or 24 hours after aspiration, groups of control, sham and experimental rats were challenged in a chamber with aerosolized *Staphylococcus aureus* labeled with radioactive phosphorus (^{32}P). Fourteen hours after bacterial challenge, intrapulmonary bacterial inactivation of the inhaled inoculum was determined.[10,11] Normal rats will inactivate approximately 90% of a bacterial challenge by 14 hours.[10,25]

The method of quantifying intrapulmonary bacterial inactivation in the rat has been previously described.[10,11,16,21] This method consisted of culturing *Staphylococcus aureus* (FDA 209 P, phage type 42 D) for 16–20 hours at 37 C in a phosphate free broth to which radioactive phosphorous had been added.[11] The bacterial culture was then washed free of non-incorporated radiotracer and resuspended in isotonic saline. Control, sham and experimental rats were placed in compartments made of wire mesh and exposed for 30 minutes to nebulized, radiolabeled staphylococci delivered in an aerosal generator system.[21] Following the bacterial inoculation, rats were removed from the wire mesh compartments and placed in standard animal cages that contained food and water.

Fourteen hours after bacterial challenge, all rats were weighed and then killed with intraperitoneal sodium pentobarbital (150 mg/kg). The lungs of each rat were excised aseptically at the level of the mainstem bronchi. The left lung was fixed in buffered 10% formalin and then sectioned and stained with hematoxylin and eosin and also with phosphotungstic acid-hematoxylin. The entire right lung was homogenized in four milliliters of nutrient broth and replicate pour plate cultures of appropriate dilutions of each homogenate were prepared. Viable bacterial counts were corrected for dilution and expressed as the number of bacteria in the right lung of each animal. Radioactivity of an aliquot of lung homogenate was quantified by deep well scintillation counting, corrected for dilution, background and quench, and expressed as isotope activity in the right lung of each animal. Intrapulmonary bacterial inactivation in each rat was calculated from the formula:[11,16]

$$\text{Per cent bacteria Inactivated} = 1 - \frac{\left(\dfrac{\text{bacterial count}}{^{32}\text{P count}}\right)(\text{lung})}{\left(\dfrac{\text{bacterial count}}{^{32}\text{P count}}\right)(\text{aerosol})}$$

Lung Water

Lung water was determined in additional groups of control, sham and experimental rats that had their left upper lobe (LUL) removed at the same time intervals that intrapulmonary bacterial inactivation studies were performed (15 and 38 hours after aspiration). The left upper lobe wet and dry (48 hours at 60 C) weights were determined and lung wet weight (LUL/animal weight), water content (wet-dry weight LUL/animal weight), and fractional water content (wet-dry weight LUL/wet weight LUL) were calculated. The animal weight at 15 or 38 hours after preparation was used as the reference weight to calculate lung wet weight and water content.

Arterial pH, pCO_2 and pO_2

Another group of control, sham and experimental rats had arterial pH, pCO_2 and pO_2 measured at 15 or 38 hours after aspiration. Arterial samples were taken from conscious rats two hours after placement of a PE 50 catheter in the right carotid artery.[25,26]

Viable Macrophages Recovered by Bronchial Lavage

Mononuclear cells were recovered from the lung by lavage in an additional group of rats 15 or 38 hours after aspiration. After the rats were anesthetized with intraperitoneal pentobarbital (50 mg/kg), their tracheas were surgically exposed and cannulated with PE 190 catheters. Ten ml of heparinized saline (1.25 units heparin/ml saline, 23 C) were slowly instilled into the lung and left there for 60 seconds. The airway fluid was then recovered and four additional 10 ml lavages were performed without the initial 60 second delay. Approximately 48–49 ml of lavage fluid were recovered in this manner and then centrifuged under refrigeration (15 C) at 600 g for 10 minutes. Two ml of supernatant were removed and returned to the test tube after the rest of the supernatant was poured off and the cells were then resuspended. A smear of the recovered cells was made and stained with blood film solutions (Solutions 1 and 2, Hemal Stain Co.) for a differential count. One ml of the cell suspension and 1 ml 0.4% trypan blue were then mixed and total cell counts and number of viable cells (supra-vital staining with trypan blue)[2,14] were simultaneously quantified on a hemacytometer.

Pulmonary Morphology

The left lung was removed from control, sham and experimental rats at the time of the bacterial inactivation

TABLE 1. *Intrapulmonary Bacterial Inactivation* (mean ± S.E.)

	Control	Intratracheal Saline	Intratracheal Blood	Probability C vs S	Probability C vs B
15 Hours After Preparation					
N	16	16	15		
Weight (g)	150 ± 6	154 ± 5	150 ± 5	>.6	>.9
14 Hour Bacterial Inactivation (%)	90.5 ± 0.7	89.0 ± 0.9	52.4 ± 8.6	>.2	<.001
38 Hours After Preparation					
N	16	11	15		
Weight (g)	167 ± 8	179 ± 6	178 ± 7	>.2	>.3
14 Hour Bacterial Inactivation (%)	89.8 ± 0.8	86.3 ± 1.9	52.3 ± 7.7	>.05	<.001

study. In addition, another group of rats had both lungs removed 15 or 38 hours after aspiration. The latter group was anesthetized with intraperitoneal pentobarbital. The trachea was exposed and clamped during inspiration. Inflated lungs were removed intact and fixed in formalin. Multiple sections were taken from each lung, and stained with hematoxylin and eosin and also with phosphotungstic acid-hematoxylin.

Ultrastructural alterations of pulmonary parenchyma were studied in five rats fifteen hours after aspiration of blood. Approximately 50 blocks of tissue from each rat were prepared as previously described.[27] After thick sections (.1 μ) were viewed by light microscopy, representative blocks from each rat were then used for preparation of ultrathin sections which were examined with the electronmicroscope.

Analysis of Data

Numerical data are expressed as a mean plus or minus the standard error of the mean. Statistical significance was determined by the t test for unpaired data.

Results

Bacterial Inactivation

Rats that were challenged with radiolabeled *Staphylococcus aureus* one or 24 hours after intratracheal injection of blood had significant impairment of intrapulmonary bacterial inactivation (Table 1). Intratracheal injection of saline had no effect on intrapulmonary bacterial inactivation.

Lung Water

Intratracheal injection of saline had no effect on left upper lobe wet weight or total or fractional water content (Table 2). However, lung water was affected by the intratracheal injection of blood. Fifteen hours after aspiration of blood, fractional water content was significantly decreased. Thirty-eight hours after aspiration of blood, left upper lobe wet weight and total water content were increased and fractional water content was decreased (Table 2).

TABLE 2. *Lung Water*

	Control	Intratracheal Saline	Intratracheal Blood
15 Hours			
N	11	13	13
Weight (g)	249 ± 7	260 ± 14	243 ± 9.0
$\frac{\text{LUL Wt}}{\text{Animal Wt}}$ (mg/g)	2.20 ± 0.25	1.98 ± 0.16	2.52 ± 0.15
$\frac{\text{W} - \text{D}}{\text{Animal Wt}}$ (mg/g)	1.77 ± 0.20	1.59 ± 0.13	1.98 ± 0.12
$\frac{\text{W} - \text{D}}{\text{W}}$ (%)	80.4 ± 0.5	80.4 ± 0.4	78.7 ± 0.3*
38 Hours			
N	12	14	14
Weight (g)	211 ± 6	211 ± 9	200 ± 4
$\frac{\text{LUL Wt}}{\text{Animal Wt}}$ (mg/g)	2.10 ± 0.09	2.02 ± 0.07	2.72 ± 0.10†
$\frac{\text{W} - \text{D}}{\text{Animal Wt}}$ (mg/g)	1.70 ± 0.07	1.63 ± 0.05	2.17 ± 0.09†
$\frac{\text{W} - \text{D}}{\text{W}}$ (%)	80.8 ± 0.2	80.5 ± 0.3	79.9 ± 0.2*

LUL = left upper lobe
W = LUL wet wt
D = LUL dry wt

* p <.01 (vs control)
† <.001

TABLE 3. *Intratracheal Fluid and Arterial pH, pCO$_2$ and pO$_2$*

		15 Hour			38 Hour	
	Control	Saline	Blood	Control	Saline	Blood
N	13	14	13	10	10	10
pH (units)	7.44 ± 0.02	7.45 ± 0.01	7.41 ± 0.01	7.42 ± 0.01	7.43 ± 0.02	7.43 ± 0.01
pCO$_2$ (mm Hg)	31.5 ± 1.6	29.1 ± 1.4	34.0 ± 1.4	35.0 ± 1.3	35.2 ± 1.1	35.5 ± 0.8
pO$_2$ (mm Hg)	79.8 ± 1.1	77.9 ± 1.2	77.4 ± 2.7	78.3 ± 1.9	81.7 ± 1.4	82.7 ± 2.5

Arterial pH, pCO$_2$ and pO$_2$

Intratracheal injection of saline or blood had no significant effect on arterial pH, pCO$_2$ and pO$_2$ (Table 3).

Macrophage Viability

When stained smears of cells recovered by lavage were examined, 95–98% of cells on each slide were monocytes. Cells recovered by lavage were not decreased in number or less viable after intratracheal injection of saline or blood (Table 4).

Pulmonary Morphology

After intratracheal injection of saline, no pulmonary morphological changes could be detected by light microscopy, whereas, after intratracheal injection of blood, focal histological abnormalities were observed. In lungs containing aspirated blood, areas of normal parenchyma were interspersed with areas of alveolar consolidation containing a few nonobstructed alveolar ducts. Even in areas of marked consolidation, patent alveolar ducts were present that might permit bacteria to reach alveoli and ducts containing aspirated blood (Fig. 1). In areas of the lung where aspiration of blood was minimal, there were many patent alveolar ducts that would allow bacteria access to the aspirated blood components (Fig. 2). Mononuclear cells predominated the inflammatory response to aspirated blood. However, some polymorphonuclear leukocytes were also present. Thirty-eight hours after aspiration of blood, degenerative erythrocytes appeared to be decreased in number but the areas of consolidation were as severe as at 15 hours.

Ultrastructural examination of the lung revealed alveolar ducts and saccules partially occluded with debris consisting of hemoglobin crystals, various free cytoplasmic organelles and other components of aspirated blood (Fig. 3). In many cases, hemoglobin crystals were found in close apposition to alveolar walls and often adjacent to damaged Type I pneumonocytes. There was an abundance of monocytes within alveolar capillaries and of macrophages within alveolar sacs. The macrophages contained a variety of material including hemoglobin crystals and inclusion whorls (Figs. 4 and 5).

Discussion

Intrapulmonary inactivation of inhaled bacteria was significantly impaired after intratracheal injection of blood. The reduced bactericidal activity was not related to systemic hypoxia, acidosis or to decreased number or viability or recovered macrophages. Focal areas of consolidation occurred within the lung following aspiration. Bacterial replication may have exceeded inactivation in areas within or adjacent to the consolidation. The presence of hemoglobin crystals in the lung may have accounted for impaired intrapulmonary bacterial inactivation since hemoglobin will impair peritoneal macrophage phagocytosis *in vivo*[3,7,28] and *in vitro*.[1] Lung water content, wet weight and dry weight increased following aspiration of blood. However fractional lung water content decreased and dehydration of macrophages may have contributed to the impaired *in vivo* antibacterial activity of the lung.[25]

Pulmonary consolidation of different etiologies has been associated with varying responses of the lung to a bacterial challenge. When consolidation was produced by viral infection in the mouse, intrapulmonary bacterial inactivation was impaired.[16] On the other hand, when

TABLE 4. *Intratracheal Fluid and Recovered Macrophages*

	Control	Saline	Blood
15 Hour			
N	10	10	10
Total cells (×10^6)	2.2 ± 0.4	1.8 ± 0.4	3.9 ± 0.9
Non-viable cells (%)	4.2 ± 0.8	3.7 ± 0.8	3.3 ± 0.6
38 Hour			
N	10	10	10
Total cells (×10^6)	2.9 ± 0.5	3.3 ± 0.4	3.5 ± 0.3
Non-viable cells (%)	2.9 ± 0.3	3.3 ± 0.7	2.0 ± 0.2*

* p (vs control) <.05

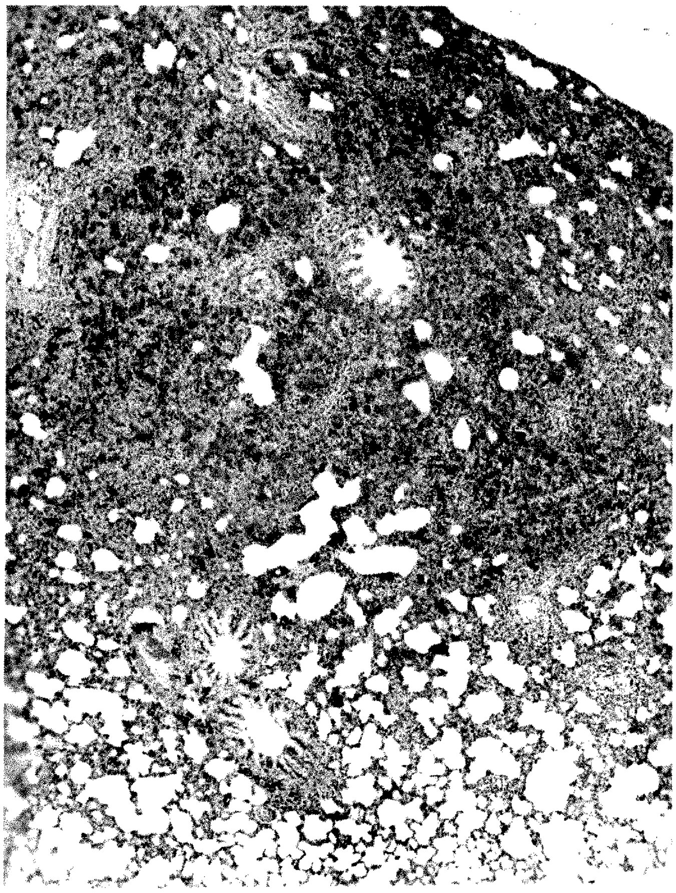

FIG. 1. Area of aspirated blood with adjacent ventilated alveoli. Non-obstructed alveolar ducts and broncholes present throughout the consolidated area (×40).

pulmonary consolidation and fluid accumulation were produced by tuberculin hypersensitivity pneumonitis in the guinea pig, an accelerated host defense occurred.[18] In the latter instance, fewer bacteria may have been deposited in the consolidated areas[12] and metabolically activated macrophages were present in increased numbers because of prior sensitization.[22] Thus, pulmonary host defenses would be normal despite the presence of abnormal morphology. In the present study, pulmonary consolidation from aspirated blood was associated with impaired intrapulmonary bacterial inactivation. Since some alevolar ducts were present within the consolidated areas, bacteria would be deposited within the aspirated blood. Once bacteria were deposited in the consolidated area, impaired inactivation and accelerated replication of bacteria may occur for several reasons. The macrophages were filled with phagocytized blood components and this may competitively impair bacterial phagocytosis. Hemoglobin or other blood components may depress bacterial phagocytosis.[3,7,28] Blood components also impair the function of alveolar surface active material.[29] Since the surfactant fraction is needed for normal *in vitro* bacterial activity of the alveolar macrophage,[19] it is possible that blood may *in vivo* alter the surface active fraction and impair bactericidal activity of the macrophage. The intra-alveolar blood components also may provide a media which is favorable to bacterial growth.

The wet weight of the lung was increased following aspiration of blood but fractional water content decreased. The increased lung weight was due to aspiration of blood and the morphological reaction to it. The decrease in lung water could be due to lysis of aspirated cells and transport of cell water away from the consolidated area. When fractional lung water content was decreased by 38 hours of dehydration, there was a direct relationship between lung water and bacterial inactivation.[24] Although the mechanism for decreased fractional lung water content in that study is different than for dehydration induced by aspiration of blood, it is possible that with aspiration of blood decreased fractional water content of the lung affects macrophage motility or its ability to engulf and subsequently destroy ingested particles.

The clinical implication of this study is apparent. If the comatose or injured patient with aspiration of blood

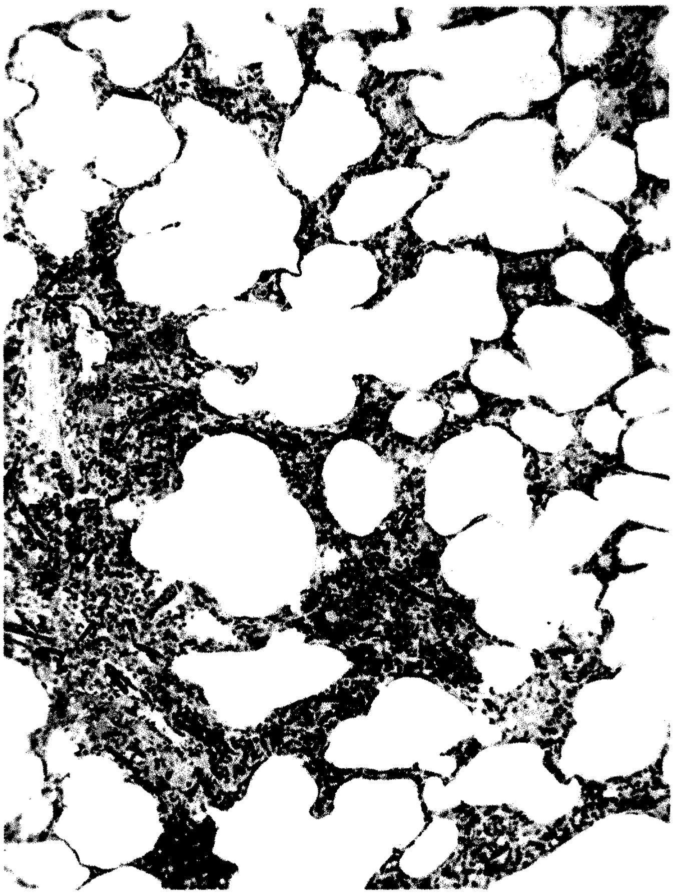

FIG. 2. Focal area of alveolar consolidation from aspirated blood. Many patent alveolar ducts and saccules are also present (×130).

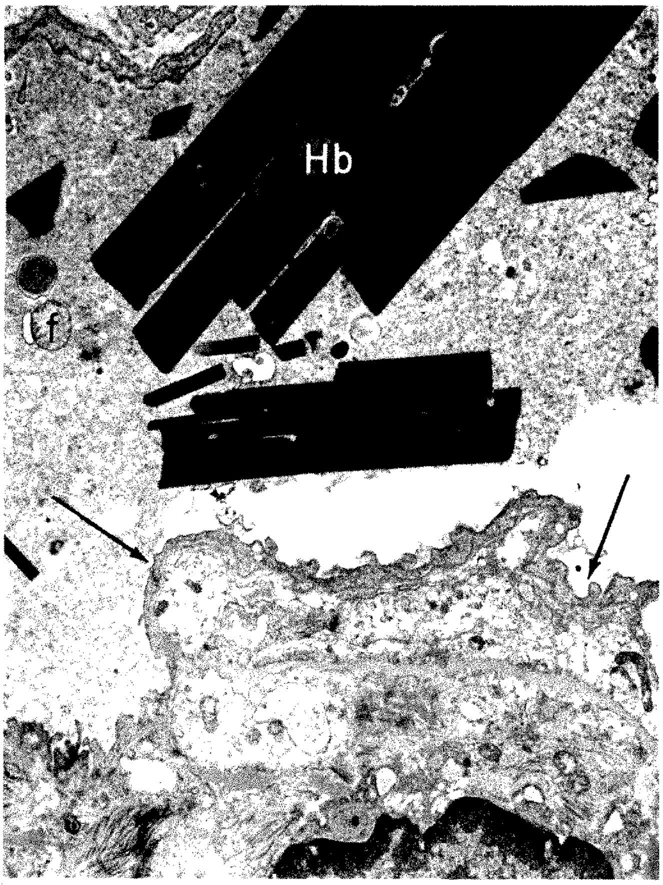

FIG. 3. Alveolar duct containing hemoglobin (Hb) crystals, cell fragments (F) and plasma proteins. Duct wall (arrow) (×10,000).

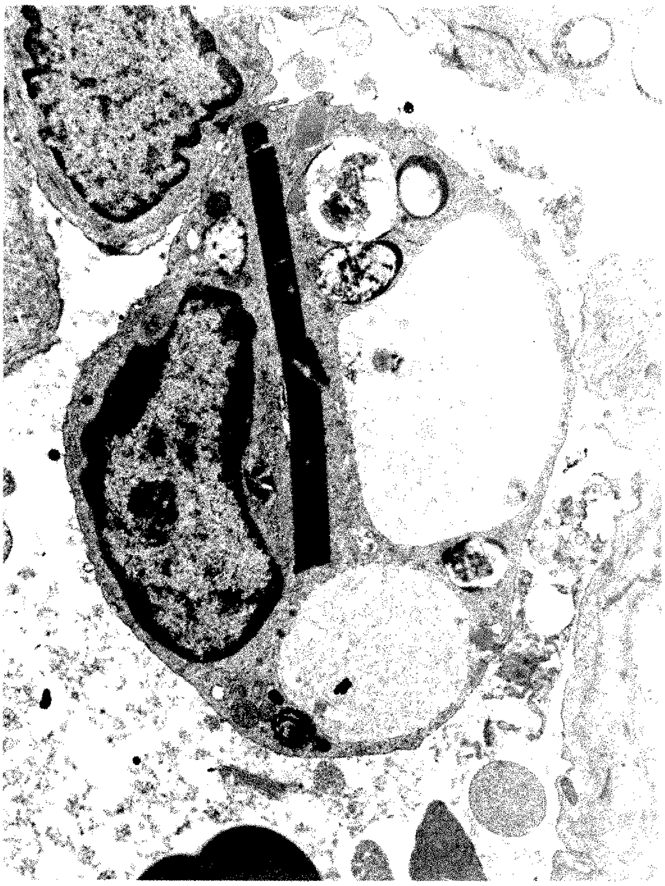

FIG. 5. Alveolar macrophages with phagocytized hemoglobin crystal and two large vacuoles containing proteinaceous debris (×11,000).

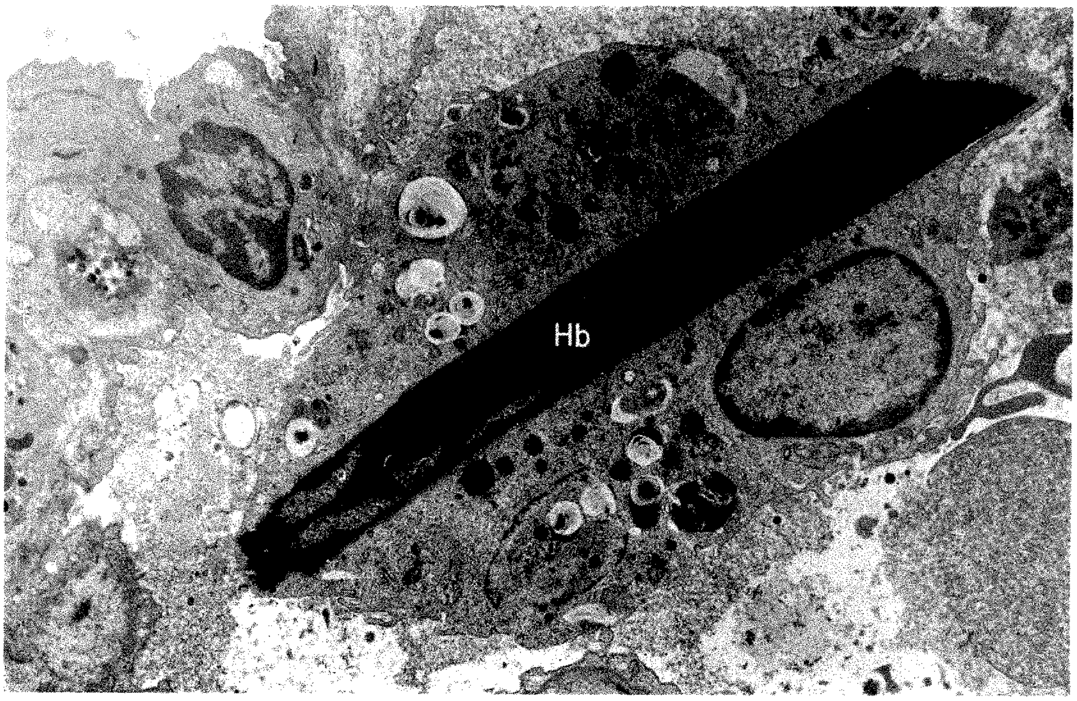

FIG. 4. Alveolar macrophage with phagocytized hemoglobin (Hb) crystal. Several inclusion whorls are also present (×5600).

or contused lung has impaired intrapulmonary bacterial inactivation similar to that demonstrated in this study, their susceptibility to pulmonary infection would be significantly increased. Whether aspiration of blood is as serious as aspiration of acid or other materials in the human is not known.[13,23] In a report of injured patients from Viet Nam, aspiration of blood following maxillofacial injuries resulted in less pulmonary impairment than aspiration of gastric contents.[22] However, aspiration was documented in only one of seven patients after maxillofacial injury and in three of seven patients with trauma of an unspecified nature. The presence or absence of additional injuries in the patients with maxillofacial injuries also was not described. Studies in the rodent have shown impaired *in vivo* intrapulmonary bacterial inactivation with hypotension,[25] hypoxia,[12] acidosis,[10] renal failure,[10] dehydration,[25] pulmonary edema[20] and oxygen toxicity.[15] If any of these factors are also present in combination with intra-alveolar blood in the injured patient, one would expect further impairment of host responses to intrapulmonary bacteria.

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Inhibition of Heidenhain Pouch Pepsin Secretion by Commercial Cholecystokinin and Duodenal Fat in Dogs

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In unanesthetized dogs with Heidenhain pouches and separated duodenal pouches, intravenous infusion of commercial cholecystokinin (1.0 IDU per min) produced a significant depression of pouch acid and pepsin secretion stimulated by pentagastrin (1.0 μg per min) or by methacholine (2.0 μg per min). Acid response to methacholine was temporarily augmented. Irrigation of the duodenal pouches with emulsified fat produced similar patterns of depression of acid secretion in response to pentagastrin and pepsin secretion in response to pentagastrin or methacholine. Acid secretion stimulated by methacholine was temporarily augmented after the irrigation. It is concluded that fat releases endogenous cholecystokinin from the duodenal mucosa and that cholecystokinin, or duodenal fat, powerfully depresses Heidenhain pouch pepsin secretion in dogs. The involvment of the gastric inhibitory polypeptide (GIP) cannot be assessed from the present experiments.

IN 1929 FENG AND COWORKERS[7] demonstrated that the intraduodenal instillation of fat depressed acid secretion from autotransplanted gastric pouches in response to a meal. The presence of fat in the duodenum powerfully contracts the gallbladder[8] and stimulates secretion of pancreatic enzymes.[20] Since a duodenal hormone, cholecystokinin-pancreozymin (CCK), exerts similar actions,[16] and serum CCK levels greatly increase after a fatty meal,[21] it is reasonable to conclude that CCK is released by fat. In previous studies,[13,14] we have shown that, in Heidenhain pouch dogs, CCK inhibited basal and secretin or methacholine-stimulated pepsin secretion. Conversely, Stening and Grossman[19] have reported that CCK stimulated pepsin secretion in gastric fistula dogs. Recent studies by Sjodin[18] indicate that, in Pavlov pouch dogs, CCK significantly inhibits pepsin secretion in response to a meal. Insufficient data exist on the effect of intraduodenal fat on pepsin secretion. It is obvious that further investigations are necessary to determine the effect of exogenous and endogenous CCK on pepsin secretion. In dogs with Heidenhain pouches and separated duodenal pouches, we investigated the effects of CCK and the irrigation of duodenal pouches with fat on acid and pepsin secretion induced by pentagastrin or methacholine.

Materials and Methods

Five dogs weighing 16–17 kg were anesthetized with sodium pentobarbital (25–35 mg per kg) and were surgically prepared with Heidenhain pouches. A separated duodenal pouch was constructed from the segment between the pyloric sphincter and the orifice of the duct of Wirsung. The pyloric end of the duodenum was closed by suturing. Gastrointestinal continuity was reestablished by gastrojejunostomy, 30 cm distal to the ligament of Treitz. It is well known that neither secretin nor CCK is liberated by gastric acid at this point. No verification, however, was attempted in these experiments. The distal end was brought through the abdominal wall as a mucocutaneous fistula. The choledochus and the duct of Santorini were ligated and transected. The gallbladder was anastomosed to the jejunum about 10 cm

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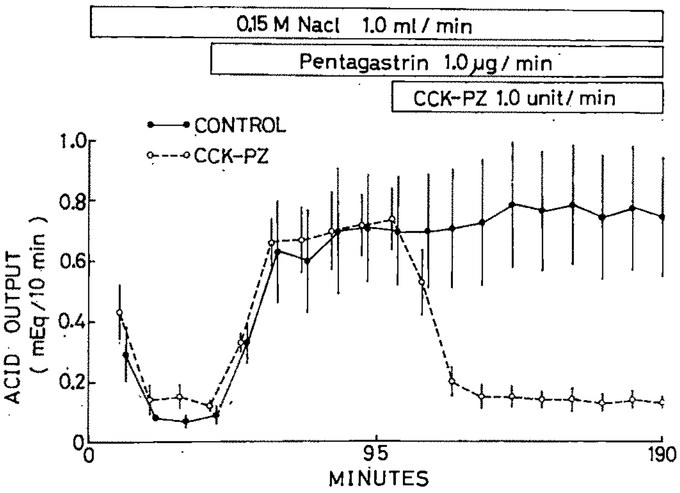

FIG. 1. Effect of cholecystokinin on acid secretion from Heindenhain pouches in response to pentagastrin. In this and subsequent figures, each point represents the mean of five experiments in 5 dogs. The vertical bars indicate the standard errors of the mean.

distal to the gastrojejunostomy. Four weeks were allowed for recovery.

The animals were fasted for 17 hr prior to the experiments. During the experiments they were held in Pavlov stands. A polyethylene catheter was threaded into a leg vein and 0.9% saline was infused at a rate of 60 ml per hr by a motor-driven syringe pump. Test substances were added to the isotonic NaCl infusion to provide the desired dosage. Heidenhain pouches were washed twice with 25 ml of isotonic NaCl before experiments were started. Isotonic NaCl (25 ml) was introduced into the Heidenhain pouch and allowed to remain there for 10 min. The fluid was collected and the pouch washed out with a further 25 ml of 0.9% NaCl at the end of each 10-min collection period. The collection and rinse were combined. A 10 ml aliquot of this was used to determine acid output by titration to pH 7.0 with 0.1 N NaOH using a Radiometer titrimeter. The remainder of the aliquot was acidified to pH 2.0 to 2.5 on collection, if needed. It was then assayed for peptic activity by the hemoglobin method.[2] Pepsin output was expressed in milligram of tyrosine per collection estimated by absorbance of the trichloracetic supernate at 280 mu.

Infusion of pentagastrin[*] (1 µg/min) or methacholine (2 µg/min) was started after three basal periods of 10 min duration. The administration of exogenous CCK[†] (1 Ivy dog unit/min) or the irrigation of duodenal pouches with fat or saline was begun 1 hr after starting the infusion of the secretagogues. To irrigate the duodenal pouches a triple-lumen Foley catheter was inserted into the pouch, which was then irrigated at a rate of 115 ml per hr. An emulsion of olive oil containing 2.5 mg of lipase powder[‡] (pork pancreas containing 1.2 lipase units per mg) and 2.5 mg of sodium taurocholate per ml was the preparation of fat used for duodenal irrigation.

Results

Intravenous infusion of CCK produced 80.5% ($P < 0.05$) and 88.4% ($P < 0.05$) mean depression of the control levels of acid and pepsin output respectively during the last seven 10-min periods of pentagastrin injection (Figs. 1&2). Acid secretion stimulated by methacholine was temporarily increased over that obtained by methacholine alone during the first four 10-min periods of CCK injection, but the difference was not significant (Fig. 3). CCK produced a 76.5% ($P < 0.05$) depression of metacholine-stimulated pepsin secretion over the last eight 10-min periods of the infusion (Fig. 4).

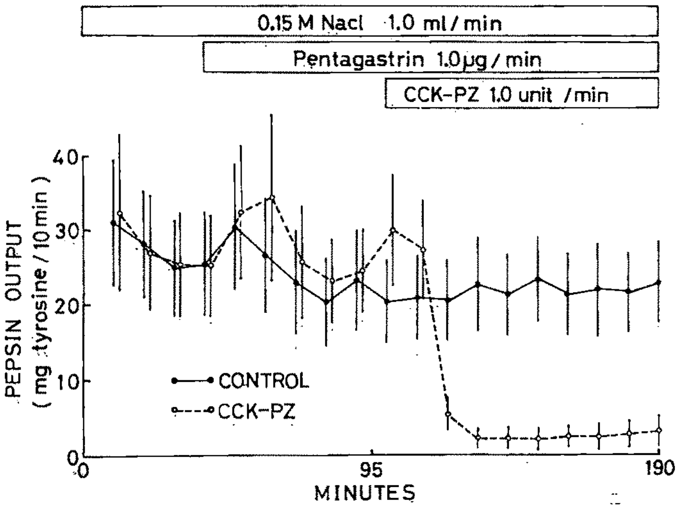

FIG. 2. Effect of cholecystokinin on pepsin secretion from Heidenhain pouches in response to pentagastrin.

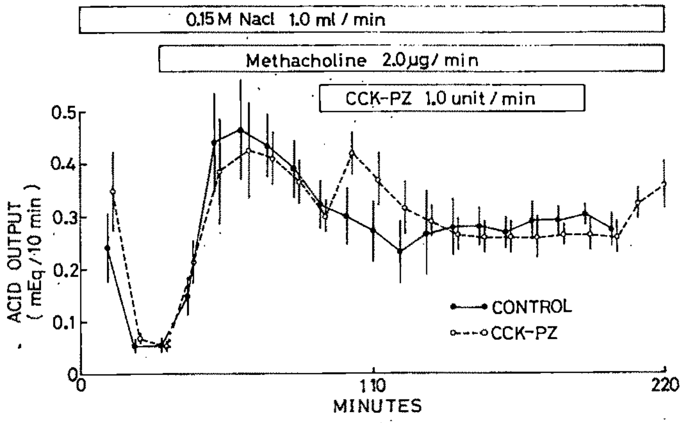

FIG. 3. Effect of cholecystokinin on acid secretion from Heidenhain pouches in response to methacholine.

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[*] Gastrin pentapeptide, Peptavalon AY-6608, donated by Ayerst Laboratories, New York, N.Y.

[†] Commercial grade obtained from GIH Research Unit, Karolinska Institute, Stockholm, Sweden.

[‡] Supplied by Mann Research Laboratories, Inc., New York, N.Y.

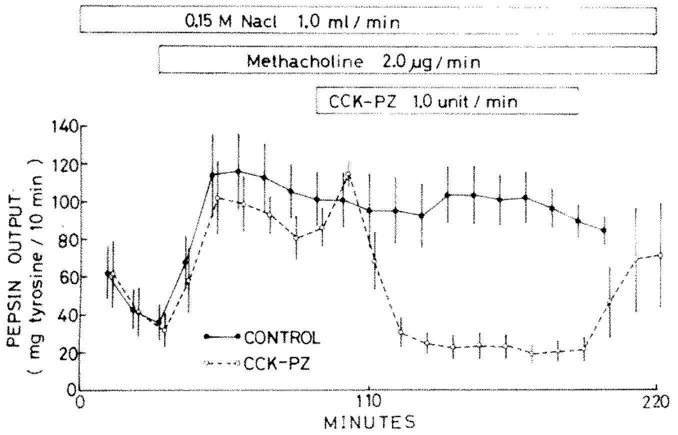

FIG. 4. Effect of cholecystokinin on pepsin secretion from Heidenhain pouches in response to methacholine.

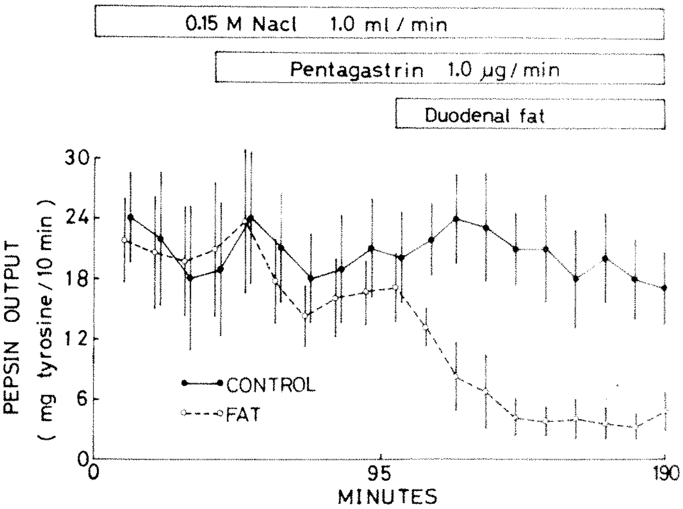

FIG. 6. Effect of the irrigation of duodenal pouches with fat on pepsin secretion from Heidenhain pouches in response to pentagastrin.

Duodenal irrigation with emulsified fat produced 32.8% (P < 0.05) mean depression of acid secretion in response to pentagastrin stimulation during the periods of the irrigation (Fig. 5) and 74.9% (P < 0.05) inhibition of pepsin (Fig. 6). Acid secretion stimulated by methacholine was temporarily increased by 53.2 to 78.4% (P < 0.05) during the first three 10-min periods of the irrigation (Fig. 7) and pepsin secretion was inhibited by 37.4 to 69.3% (P < 0.05) over the last five 10-min periods (Fig. 8).

Discussion

The effects of duodenal hormones on gastric acid secretion have been the subject of numerous communications and reviews.[9,10,16]

While CCK has been shown to inhibit pentagastrin-stimulated acid secretion in dogs and Necturus gastric mucosa *in vitro*[12,13] it behaves as a full agonist for acid secretion in cats and frog gastric mucosa *in vitro*.[4,12] The present results confirm that pentagastrin-stimulated acid secretion is depressed by both commercial CCK and intraduodenal fat and methacholine-stimulated acid secretion is temporarily augmented in dogs.[11,15] The time course of the reduction and augmentation of acid secretion by commercial CCK closely resembled the pattern of response after fat in the duodenum.

Although commercial CCK has been reported to produce significant inhibition of pepsin secretion in both denervated and innervated pouch dogs,[13,14,18] little information is available on the effect of intraduodenal fat on pepsin secretion. In 1934, Alley *et al.*[1] reported that fat reduced pepsin secretion more than acid secretion in dogs. The data presented demonstrate that both commercial CCK and intraduodenal fat significantly inhibit pepsin secretion in pentagastrin- or methacholine-stimulated Heidenhain pouch dogs.

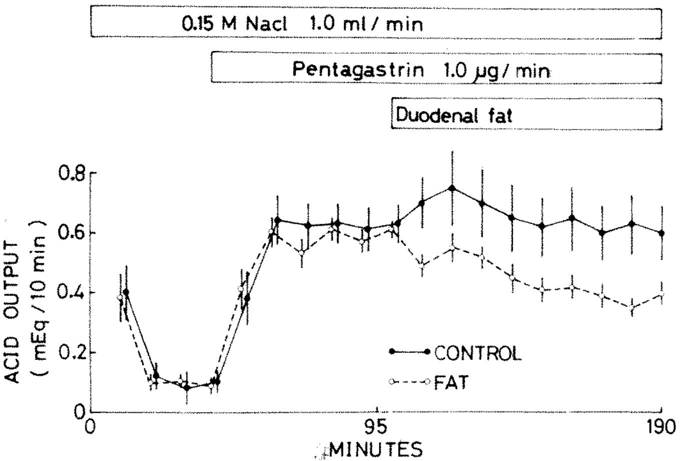

FIG. 5. Effect of the irrigation of duodenal pouches with emulsified fat on acid secretion from Heidenhain pouches in response to pentagastrin.

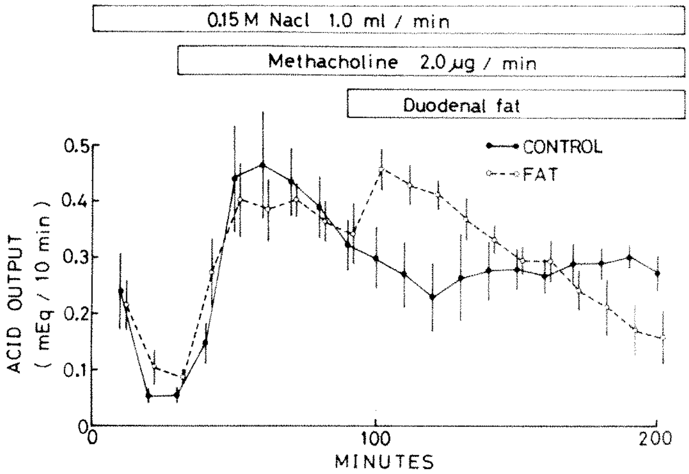

FIG. 7. Effect of the irrigation of duodenal pouches with fat on acid secretion from Heidenhain pouches in response to methacholine.

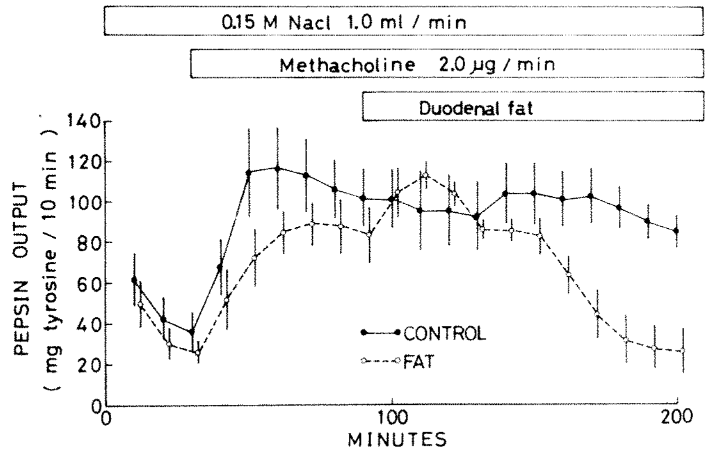

Fig. 8. Effect of the irrigation of duodenal pouches with fat on pepsin secretion from Heidenhain pouches in response to methacholine.

The gastric inhibitory polypeptide (GIP) isolated from a partially purified commercial CCK preparation by Pederson and Brown[17] inhibited acid and pepsin secretion induced by pentagastrin, histamine, methacholine[11] or insulin hypoglycemia in dogs. Since GIP may not contract the gallbladder or provoke pancreatic enzyme secretion[3] it is uncertain at present whether GIP is liberated by intraduodenal fat in physiologically significant amounts, but it is contained in the commercial CCK which we have used.

Fara and coworkers[5,6] demonstrated that, in cats, the intraduodenal instillation of fat produced an increase in superior mesenteric blood flow, gallbladder pressure, duodenal motility and pancreatic enzyme output, which could be closely mimicked by an intravenous infusion of CCK. In the same species, Deveney and Way[4] found that the introduction of fat into the duodenum of cats, like the intravenous administration of CCK, increased acid secretion unstimulated or stimulated by pentagastrin or histamine. Recently Young *et al.*[21] have found that serum CCK levels markedly increase after a fatty meal in man, and Magee and Dutt[11] have shown that pure CCK depressed Heidenhain pouch pepsin after either methacholine or pentagastrin. On the basis of these experimental results including the results presented, we conclude that fat liberated endogenous CCK from the duodenal mucosa and that fat is a potent inhibitor of gastric pepsin secretion from Heidenhain pouches in dogs as are both commercial and pure CCK. From the present experiments the role played by GIP either following fat or commercial CCK cannot be assessed.

Acknowledgment

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Retained Biliary Calculi:

Removal by a Simple Non-operative Technique

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Ten patients with retained biliary calculi demonstrated by postoperative T-tube cholangiography were managed by a simple nonoperative washout technique. The bile was cultured routinely before each group of washouts, since fever was a common sequel in the presence of infected bile. After a parenteral dose of propantheline bromide, the biliary tree was flushed through the T-tube with 1 litre of normal saline containing 40 ml of lignocaine. Progress was followed by T-tube cholangiography, and the criterion of success was a cholangiogram showing adequate filling of the biliary tree, absence of filling defects, and free flow of contrast medium into the doudenum. The technique was successful in six of the ten patients. There was no mortality and no significant morbidity.

The routine use of intraoperative cholangiography has reduced the incidence of retained biliary calculi following cholecystectomy and bile duct exploration, but calculi are still demonstrated in a significant number of cases by postoperative cholangiography.[1,9,12,14] Removal of the draining T-tube in the hope that the stones will pass spontaneously or cause no further trouble has proved unsatisfactory, since 8 out of 10 patients develop symptoms or complications requiring re-exploration.[3] Such reoperation is associated with a significant mortality and morbidity, and the chances of finding and removing residual calculi fall progressively with the second and each subsequent exploration.[5,13]

Various nonoperative techniques for dealing with retained calculi have been proposed, including chemical dissolution, flushing with a variety of solutions, and extraction with instruments or catheters passed down the T-tube track,[2,4,6-8,10,11,14] but none of these methods has found wide acceptance. In 1967, Hivet and Richarme[4] reported five cases in which calculi were successfully washed out of the ducts by a simple saline flush. This report describes a modification of this technique, and its application in ten patients with retained bile duct stones.

Materials and Methods

In the three-year period from January 1970 to December 1972, nine partients were found to have retained biliary calculi following cholecystectomy and exploration of the common bile duct in the University Surgical Unit at the Princess Alexandra Hospital, Brisbane. A tenth patients was referred from another unit in the same hospital.

In each patient, aerobic and anaerobic cultures of the bile were undertaken at 7 days, and routine T-tube cholangiography was performed at intervals of from 9 to 12 days after the primary procedure. Following the radiological demonstration of residual calculi, propantheline bromide was administered intramuscularly 30 minutes before flushing of the bile ducts with 1 litre of sterile 0.9% saline at room temperature containing 40ml of 1% lignocaine, suspended 1 m above the mid axillary line. The saline bottle was connected to the T-tube through a standard intravenous administration set, and the infusion was started slowly, since all patients experienced initial discomfort. As this subsided, the solution was allowed to flow as rapidly as possible. The patient's position was altered to direct the stream into all parts of the biliary tree in an attempt to dislodge the calculi. Three

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washouts were given at daily intervals, and the T-tube was clamped after each procedure. If the patient developed pyrexia, the tube was immediately released, and free drainage of the biliary system re-established. Results were assessed by further T-tube cholangiography prior to removal of the T-tube. Success was indicated by a post-washout cholangiogram showing adequate filling of the biliary tree, no filling defects, and free flow of the contrast medium into the duodenum.

Case Reports

Case 1. D.T., a 65-year-old woman, was admitted on April 22, 1970 with obstructive jaundice, ascending cholangitis, and an *E.coli* septicemia. Cholecystectomy had been carried out 10 years previously in another hospital. The patient did not respond to conservative treatment, and the bile ducts were explored on April 24, 1970. Soft stones and biliary mud were removed from a dilated duct system. Completion cholangiography through a T-tube suggested at least two further calculi in the common hepatic duct, but the patient's condition was so poor at this stage that further exploration was not performed. The patient made a good recovery, and on the 12th postoperative day, a further T-tube cholangiogram confirmed the presence of two residual calculi. Bile culture showed a growth of mixed enteric organisms. Washouts were carried out daily on three occasions from the 20th day, each washout being associated with mild initial discomfort, acute attacks of right upper quadrant pain, and low grade post washout fevers. On a post washout cholangiogram, the smaller (10 × 5mm) of the two calculi could no longer be demonstrated, but the larger (14 × 10mm) calculus was still present. Before any further washouts could be performed, the patient accidentally stepped on the T-tube while getting out of bed and dislodged it. Following a further attack of cholangitis re-exploration of the common bile duct was performed. Six months after the initial episode the patient was readmitted with a locally invasive cystadenocarcinoma of the ovary, which was treated by panhysterectomy and removal of an involved segment of pelvic colon. At present she is free of biliary symptoms, although there is evidence of local extension of the carcinoma.

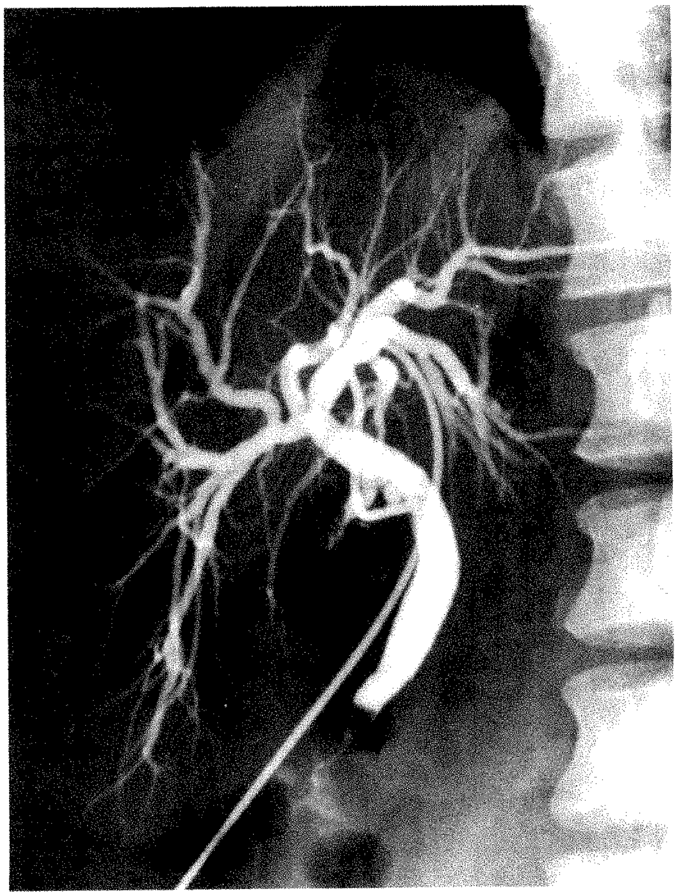

FIG. 1. Ten-day cholangiogram in Case 4 showing a 7 × 7 mm calculus at the lower end of the common bile duct.

Case 2. L.C., a 58-year-old man, underwent cholecystectomy on May 5, 1970 following an acute attack of cholecystititis. The gall bladder contained multiple faceted calculi and an operative cholangiogram demonstrated a dilated duct system. No stones were found on exploration, and no completion cholangiogram was performed. Bile culture in the postoperative period was sterile. A 10-day T-tube cholangiogram demonstrated a solitary calculus 9 × 7 mm in size at the lower end of the common bile duct. Three washouts were performed, each accompanied by some initial discomfort, but no colic and no post washout fever. Repeat cholangiogram showed no change, and the calculus was removed at a second operation. The patient remains well with no further symptoms.

Case 3. C.F., a 20-year-old woman, had suffered from repeated attacks of biliary colic prior to cholecystectomy on April 5, 1971. The gall bladder contained multiple small calculi, and an operative cholangiogram demonstrated multiple calculi in the common mile duct and common hepatic duct. Twenty-five small calculi were removed on exploration of the duct system. The completion cholangiogram was of poor quality, but was interpreted as showing no abnormality. The 10-day cholangiogram demonstrated at least 11 small defects scattered throughout the bilitary tree. These were initially interpreted as air bubbles, but remained constant on two further cholangiograms. The largest of the defects was 5 × 5 mm, and the smallest 2 × 2 mm. Bile culture showed a growth of mixed enteric organisms. Over the next 53 days, 13 washouts progressively cleared these defects, now definitely considered to be calculi. The patient experienced initial discomfort and recurring attacks of right upper quadrant pain, high fever, rigors and diffuse myalgia with each washout. Each febrile episode subsided rapidly on unclamping the draining T-tube. No antibiotic therapy was utilised. The final T-tube cholangiogram was interpreted as showing no evidence of residual calculi, and the T-tube was removed. Two small stones 2 × 2 mm in size were found in the short limb of the T-tube, and in retrospect, these calculi can be seen on the final cholangiogram. The patient has had no further biliary symptoms.

Case 4. A.A., a 47-year-old woman, had suffered from recurrent episodes of biliary colic and was submitted to cholecystectomy on September 13, 1971. The gall bladder contained multiple small calculi, and an operative cholangiogram demonstrated multiple calculi in the bile ducts. On exploration, 14 small stones were found and removed from the biliary tree. No completion cholangiogram was performed. Bile cultures demonstrated a growth of mixed enteric organisms. A 10-day cholangiogram (Fig. 1) showed a 7 × 7 mm calculus at the lower end of the common bile duct. This calculus was successfully cleared after a series of three washouts (Fig. 2). With each washout, the patient developed initial discomfort, several episodes of acute right upper quadrant pain, but no post washout fever. The patient has had no recurrence of biliary symptoms.

Case 5. A.R., a 74-year-old woman, presented on September 16, 1971 with obstructive jaundice and mild cholangitis. Cholecystectomy and choledocolithotomy had been carried out at another hospital 7 years previously. The patient was treated conservatively and a later intravenous cholangiogram showed two large calculi at the lower end of the common bile duct. Exploration was carried out on October 4, 1971, one large calculus being removed while a second large soft calculus fragmented during removal. Completion cholangiogram was of poor quality but was accepted as showing no abnormality. Bile cultures showed a growth of mixed enteric organisms. A 10-day T-tube cholangiogram demonstrated multiple defects varying in size from 8 × 8 mm to 2 × 2 mm, which were presumed to be due to fragments of the second large calculus, and which were still present on a 12-day cholangiogram. Four washouts were given at daily intervals from the 12th day, each washout being accompanied by initial discomfort, acute exacerbations of right upper quadrant pain, and mild post washout fever. The final cholangiogram showed no evidence of residual calculus. The patient has had no recurrence of biliary symptoms.

Case 6. E.R., an 82-year-old woman, was admitted on May 28, 1972 with acute cholecystitis. After 24 hours of conservative management, increase in local and systemic signs lead to laparotomy, when an acutely inflammed gall bladder containing multiple faceted calculi, and with a perforation of the fundus was found. A large calculus could be palpated in the common bile duct and its presence was confirmed on the operative cholangiogram. Cholecystectomy was carried out, and a single large calculus was removed from the common bile duct. The completion cholangiogram was of poor quality, but was not repeated in view of the patient's poor general condition at this stage of the operation. Bile cultures demonstrated a growth of mixed enteric organisms. A 10-day T-tube cholangiogram demonstrated a 10 × 5 mm filling defect. A single washout was carried out under image intensifier control on the 17th postoperative day. The calculus was visualised initially at the lower end of the common bile duct, but was no longer visible at the end of the procedure. This washout was accompanied by mild initial discomfort, severe acute pain in the right hypochondrium, and a mild post washout fever. A T-tube cholangiogram 2 days later showed no evidence of residual calculus. The patient has had no recurrence of biliary symptoms.

Case 7. N.W., a 79-year-old woman, was admitted with a history of recurrent episodes of biliary colic. At operation on September 24, 1972 the gall bladder was found to contain multiple facetted stones and was removed. The duct system was moderately dilated and several calculi were seen at the lower end of the common bile duct on the operative cholangiogram. Nine calculi were removed during exploration of the duct system. Completion cholangiogram showed no evidence of passage of contrast medium into the duodenum, and there appeared to be some deformity of the lower end of the common bile duct. Transduodenal sphincterotomy and re-exploration of the duct were therefore performed, but no further calculi were found. No final completion cholangiogram was performed. Bile cultures showed a growth of mixed enteric organisms. A 12-day cholangiogram demonstrated a 10 × 3 mm calculus at the lower end of the common bile duct. A single washout was carried out on 17th postoperative day, and was accompanied by initial discomfort, multiple attacks of acute right upper quadrant pain, and mild post washout fever. A final cholangiogram showed no evidence of residual calculus. The patient has had no recurrence of biliary symptoms.

Case 8. H.C., an 80-year-old woman, had suffered many attacks of cholecystitis associated with jaundice in the six months prior to cholecystectomy on December 19, 1972. At operation, the gall bladder contained multiple calculi, and two stones were palpable in the common bile duct. Six small stones were removed on exploration of the duct system, and the completion cholangiogram was interpreted as showing no abnormality. Bile culture showed a growth of mixed enteric organisms. The 10-day cholangiogram showed several small defects which were interpreted as air bubbles, but one defect, measuring 8 × 6 mm, was still apparent at the junction of the right and left hepatic ducts on a further cholangiogram. A washout was performed under image intensifier control on the 20th postoperative day. The calculus was visualised initially in the left hepatic duct and subsequently below the T-tube at the lower end of the common bile duct. This washout was accompanied by mild initial discomfort and severe acute pain radiating from the epigastrium to the back but no post washout fever. Further washouts on each of the next 2 days were accompanied by initial discomfort and a low grade post washout fever, severe acute pain occurring once only in the first of these two washouts. A final T-tube cholangiogram was interpreted as showing no residual calculi, and the T-tube was removed.

However, the patient was readmitted 1 week later with biliary colic and jaundice, and a later intravenous cholangiogram showed a filling defect at the lower end of a dilated common bile duct. Review of the T-tube cholangiogram demonstrated that this stone had been apparent in the final x-rays, which were misinterpreted. A 8 × 6 mm calculus was removed at re-exploration on February 13, 1973, following which the patient has had no further biliary symptoms.

Case 9. P.F., a 21-year-old man, was admitted on December 10, 1972 with obstructive jaundice and cholangitis which failed to settle with conservative management. A percutaneous transhepatic cholangiogram on December 21, 1972 showed complete obstruction of the lower end of the common bile duct, and cholecystectomy with exploration of the bile ducts was performed on the same day. The gall bladder was edematous and contained several pigment stones. Many soft pigment stones were removed from

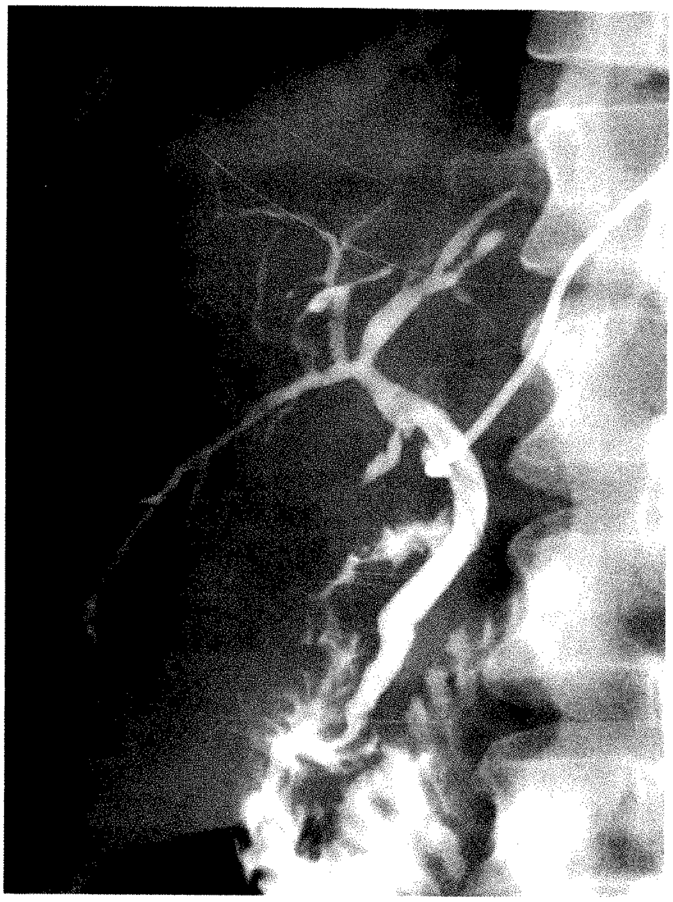

FIG. 2. Cholangiogram in Case 4 taken after a series of 3 washouts demonstrating successful clearing of the calculus.

the common bile duct, but completion cholangiogram was not performed because of peroperative hypotension. Operative bile culture showed a growth of Pseudomonas aeruginosa.

The 11-day cholangiogram and a repeat examination on day 12 showed many filling defects with the appearances of air bubbles, but a further cholangiogram on day 21 showed persistence of a single defect 5 × 4 mm in diameter, apparently impacted at the lower end of the common bile duct. A washout performed under image intensifier control on that day produced vigorous perstalsis at the lower end of the common bile duct which was associated with severe acute pain in the right hypochondrium, but no contrast medium passed into the duodenum. There was a mild post washout fever. Four further washouts carried out over the next 21 days were accompanied only by mild initial discomfort, with no severe pain or fever. A T-tube cholangiogram 4 days after the last washout showed no evidence of residual calculus. The patient has had no recurrence of biliary symptoms.

Case 10. J.G., a 71-year-old woman, had suffered from recurrent episodes of biliary colic for 3 years prior to cholecystectomy on February 6, 1973. The gall bladder contained numerous calculi, and an operative cholangiogram demonstrated several small calculi at the lower end of the common bile duct. On exploration seven smal stones 4 mm in diameter were removed from the biliary tree. Completion cholangiogram was accepted as showing no abnormality. Bile cultures showed a growth of mixed enteric organisms. A 9-day cholangiogram was not of diagnostic quality, and the examination was therefore repeated on the 20th postoperative day, demonstrating a 4 × 4 mm calculus in the common bile duct just proximal to the upper limb of the T-tube. Seven washouts were performed over the next 30 days, each accompanied by slight initial discomfort but no colic, with low grade post-washout fever following only the first. This fever subsided rapidly on unclamping the T-tube and administration of appropriate antibiotics. Further cholangiograms were performed after the second, fifth, and seventh washouts and each showed no change in the position of the calculus, which was removed at a second operation. The patient remains well, with no further symptoms.

Review of Results

The results obtained in this group of ten patients are summarised in Table 1. In three patients, the procedure was unsuccesful, and in one, misinterpretation of the cholangiogram led to retention of a calculus. In the remaining six patients, the stones were cleared by the flushing procedure. Two patients responded to a single washout, one was successful after three, one after four, one after five, and in the remaining case multiple small calculi required 13 flushing procedures over a 53-day period.

TABLE 1. *Number of Washouts and Result*

Case	No. of Washouts	Result
1	3	Unsuccessful (T-tube accidently removed)
2	3	Unsuccessful
3	13	Successful
4	3	Successful
5	4	Successful
6	1	Successful
7	1	Successful
8	3	Unsuccessful (X-ray misinterpreted)
9	4	Successful
10	7	Unsuccessful

TABLE 2. *Calculus Size, Number and Position, as Determined from the Cholangiographic Films*

Case	Largest Calculus (m.m.)	Number	Position	
1	10 × 14	2	C.B.D.	
2	9 × 7.5	1	C.B.D.	
3	5 × 5	multiple	C.B.D. L.H.D.	C.H.D. R.H.D.
4	7 × 7	1	C.B.D.	
5	8 × 8	multiple	C.B.D.	C.H.D.
6	10 × 5	1	C.B.D.	
7	10 × 3	1	C.B.D.	
8	8 × 6	1	L.H.D.	
9	5 × 4	1	C.B.D.	
10	4 × 4	1	C.B.D.	

C.B.D.	Common Bile Duct
L.H.D.	Left Hepatic Duct
R.H.D.	Right Hepatic Duct
C.H.D.	Common Hepatic Duct

The number of calculi and their size were estimated from the cholangiographic films (Table 2). In the unsuccessful group, the largest stone measured 14 × 10 mm, and the smallest 4.0 × 4.0 mm. The largest stone successfully washed out measured 10 × 5 mm, and the smallest 2 × 2 mm. In two of the successful group, calculi were present in the common hepatic duct and its radicals proximal to the T-tube, in addition to those in the common bile duct. The largest of these proximal calculi measured 3 × 3 mm and the smallest 2 × 2 mm. However, a larger proximal stone, 4 × 4 mm in size, was not washed out.

All patients experienced initial discomfort, which was easily controlled by slowing the rate of flow. Eight also complained of episodes of sharp pain in the upper abdomen with back radiation lasting from a few seconds to several minutes. In seven of these eight patients, stones were successfully washed out, although in one patient (Case 1), a further calculus remained at the enforced termination of washout therapy.

Nine of the ten patients showed a growth of mixed enteric organisms in the bile (Table 3), and eight of these developed pyrexia following the washouts. One patient developed a high fever, rigors and diffuse myalgia at the time of each procedure, but in the remaining seven, fevers were mild, and the patients were unaware of any upset. The patient with sterile bile developed no fever.

There were no residual effects, and the six patients with successful washouts have shown no evidence of residual stones at intervals of 6 months to 3 years since the procedure.

Discussion

The technique of bile duct flushing described in this report was successful in clearing residual calculi from the bile ducts in six of the ten cases treated. The morbidity associated with the procedure was of minor degree in all but one case. The initial discomfort experienced as the perfusion was started was presumably due to distention of the biliary tree, and the acute exacerbations of pain were considered to be caused by temporary obstruction of the ampulla by a calculus. Although such pain may indicate passage of a stone, clearly further T-tube cholangiography must be utilised in order to determine the success or failure of the procedure.

The fever seen in eight patients was presumed to be due to transient bacteremia from cholangio-venous reflux. It is significant that pyrexia was not seen in the single patient with sterile bile. We believe that such cholangio-venous reflux represents a potential source of more serious morbidity and perhaps even mortality, and for this reason have always cultured the bile before each group of washouts. Although appropriate prophylactic or therapeutic antibiotics were not used routinely in this series, there may be an argument for their administration, particularly in the elderly or the ill.

Two of the four failures came early in our experience, one following accidental removal of the T-tube, and the other after what we would now consider an inadequate trial of the method. The presence of the T-tube did not prevent the washout of multiple proximal stones up to 3 mm in diameter in two patients, but a 4mm diameter stone in a third patient was not cleared. We believe the retention of the T-tube offers advantages in maintenance of drainage when compared with the rather similar flushing technique described by Lamis, Letton and Wilson,[6] where the T-tube is removed after a well-defined track has been established, and a coudé tipped rubber catheter inserted. However, this technique may be of greater value with large proximal stones. The fourth failure was due to a misinterpretation of the T-tube cholangiogram, and demonstrates the importance of careful review of the radiographic appearances before final removal of the T-tube.

In the same three-year period, a further three patients in the Unit in whom there was definite clinical but equivocal radiological evidence of biliary obstruction following exploration of the common bile duct have been treated by the same technique with clinical relief of obstruction and satisfactory final cholangiography. It is not clear whether the cause of obstruction in these three patients was simple sphincter spasm, fragments of blood clot or small residual calculi, but the washouts were followed by clinical and radiological relief of obstruction.

TABLE 3. *Relationship of Bile Infection and Post-washout Fever*

Case	Infected Bile	Fever
1	yes	yes
2	no	no
3	yes	yes (rigors)
4	yes	no
5	yes	yes
6	yes	yes
7	yes	yes
8	yes	yes
9	yes	yes
10	yes	yes
	9	8

The results obtained in this small series suggest that the technique of flushing is a safe and simple one, and that it has a significant place in the management of definite retained biliary calculi, or where some doubt exists as to the presence of residual calculi. It is unlikely that it will be successful in every instance, as this series shows, but we feel that it should be used routinely before resorting to the more prolonged technique of chemical solution,[14] or surgical re-exploration.

Acknowledgments

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Elective Total Gastrectomy for Cancer of the Stomach:

End Results

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There has been no apparent improvement in overall salvage of patients with cancer of the stomach treated by *elective* extended total gastrectomy from 1950–1964 as compared with those treated by partial gastrectomy during the preceding 20-year period, 1931–1950 at Memorial Hospital in New York City. Criteria of resectability have been extended in recent years, and, therefore, the two series of patients cannot be considered strictly comparable. In the 94 patients subjected to elective total gastrectomy for cancer of the stomach, more than half (55 patients) had cancer in the proximal 1/3 of the stomach. The results obtained in this group by total gastrectomy are inferior to those obtained in the earlier series by partial gastrectomy. Patients with carcinoma of the mid 1/3 of the stomach showed essentially the same 5-year survival by elective total gastrectomy (34.8%) as by partial gastrectomy (33.5%), while those with carcinoma of the distal 1/3 of the stomach showed a greater 5-year survival by elective total gastrectomy (43.7%) than by partial gastrectomy (29.8%). However, of significance is the fact that the incidence of nodal metastasis was 3 times greater in the patients undergoing elective total gastrectomy than in those undergoing partial gastrectomy. Despite this unfavorable finding, 5-year survival in the patients undergoing elective total gastrectomy for carcinoma of the mid 1/3 or distal 1/3 of the stomach was equal to, or better than, that found in those undergoing partial gastrectomy for lesions similarly located. On the basis of this finding alone, we believe that elective total gastrectomy is a worthwhile endeavor and should be performed for operable carcinomas arising in the mid 1/3 or distal 1/3 of the stomach.

AN ANATOMICALLY more thorough operation for gastric cancer has been regularly performed at Memorial Hospital in New York City since 1950. This procedure has consisted of total gastrectomy, resection of greater and lesser omenta, splenectomy, and resection of the body and tail of the pancreas.[4] The senior author believed that gastric resection, as customarily performed in the past, was inadequate for control of most gastric cancers. This belief was sustained by a review of the course of 92 patients from the time of their "curative" resection until their death and autopsy. This review disclosed that only 4 patients had in fact been cured and that local recurrence of the cancer had developed in 74 patients, or in 4 of every 5 patients.[5]

Anatomical studies, furthermore, on surgical specimens following extended total gastrectomy, initially fixed in formalin and subsequently cleared in dioxane solution for recognition and sampling of *all* lymph nodes, revealed a high incidence of metastases in unsuspected regional lymph nodes.[6]

Sufficient time has now elapsed for evaluation of results thus obtained.

Clinical Material

During the 15-year period, 1950-1964, total gastrectomy was performed on 206 patients at Memorial Hospital. All of these operations were performed by the attending surgeons* of the Gastric Service, by the senior

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* One or more extended total gastrectomy was performed by each of the following surgeons, listed alphabetically: Robert J. Booher, Lemuel Bowden, Richard D. Brasfield (deceased), Alexander Brunschwig (deceased), Joseph G. Fortner, Walter Lawrence, Jr., Gordon NcNeer (deceased), Charles J. McPeak, Theo R. Miller, George T. Pack (deceased), Isabel Scharnagel (deceased).

TABLE 1. *Elective Total Gastrectomy for Cancer of Stomach (1950–1964)*

	Males	Females	Total
Total no. patients	128	78	206
Obligate	64	48	112
Elective	64	30	94

surgical residents under the direct supervision of these attending surgeons, or by the late Alexander Brunschwig. All the recorded data in these 206 patients have been reviewed. It was apparent that more than half of these patients were subjected to total gastrectomy as a necessary or obligatory procedure in order to encompass completely the gastric neoplasm. Furthermore, in the early years of this study occasional instances of incomplete removal of the gastric cancer by total gastrectomy were encountered, due to unwarranted enthusiasm on the part of the surgeon when faced with an almost-but-not-quite operable lesion. It was learned early in this study that total gastrectomy was rarely a justifiable palliative procedure.[1]

The intent of this paper is to determine the place for elective total gastrectomy in the management of operable gastric cancer. If 5 cm or more of the lesser curvature, either proximally or distally, is uninvolved by tumor, then subtotal resection of the stomach is at least technically possible. Both the operative report and the gross pathological findings of all 206 patients were reviewed. Ninety-four patients might have undergone subtotal rather than total gastrectomy as determined by this criterion, and thus appear to have undergone truly *elective* total gastrectomy. Further analysis will be based on these 94 patients only (Table 1).

Sex, Race and Age

There were 64 male patients and 30 female patients. There was 2 Negroes, one male and one female, but all remaining patients were Caucasian. Ages ranged from 39 years to 81 years with a median age of 63 years in the male patients and a median age of 62 years in the female patients.

Features of Operation

Total gastrectomy, with identifiable esophageal tissue proximally and duodenal tissue distally, was performed in all 94 patients. For reasons not apparent in retrospective analysis 19 of these 94 patients did not have distal pancreatectomy performed as an integral part of the procedure, and 2 of these 19 patients furthermore did not undergo splenectomy. All the remaining 75 patients had extended total gastrectomy performed, including removal of the greater and lesser omenta, the body and tail of the pancreas, and the spleen along with the entire stomach. Six of these 94 patients also had resection of transverse colon, 7 others had resection of distal thoracic esophagus, and 2 others had marginal resection of the left lobe of the liver as well (Table 2).

TABLE 2. *Elective Total Gastrectomy: Extent of Operation*

Total gastrectomy alone		19
Extended total gastrectomy		60
+ resection of colon	6	
+ resection of liver	2	15
+ resection of distal esophagus	7	
Total		94

TABLE 3. *Elective Total Gastrectomy: Reconstruction after Resection*

e-to-s Esophagojejunostomy	36
e-to-s Esophagojejunostomy with lateral (Braun) anastomosis	38
e-to-e Esophagoduodenostomy	1
Roux-Y reconstruction	15
"Pouch" reconstruction	4
	94

Reconstruction following total gastrectomy was by end-to-side esophagojejunostomy alone in 36 patients, by end-to-side esophagojejunostomy with complementary jejuno-jejunostomy in 38 patients, by esophagoduodenostomy in 1 patient, by Roux-Y esophagojejunostomy in 15 patients, and by "pouch" reconstruction (Lima Basto technique)[2] in 4 patients (Table 3).

Two patients received no blood replacement during surgery, while 2 patients required 8 units of blood each during surgery. Both the median and the average blood replacement during surgery in these 94 patients was 3 units (1500 ml).

Operating time in these 94 patients varied from 3 hours to 11 hours, with a median operating time of 6 hours.

Duration of postoperative hospitalization in the operative survivors varied from 9 days to 111 days, with a median postoperative hospitalization of 18 days (Table 4).

Pathology

Six of these 94 patients had primary lymphoma of the stomach, 5 classified as reticulum cell sarcoma, and 1 as lymphosarcoma. These were 2 primary leiomyosarcomas of the stomach and 2 epidermoid carcinomas,

TABLE 4. *Elective Total Gastrectomy: Median Values*

Median age 63 yrs. (males)	62 yrs. (females)
Operating time	6 hours
Blood replacement	1500 ml
P.O. hospitalization (in operative survivors)	18 days

TABLE 5. *Elective Total Gastrectomy: Pathology*

Gastric lymphoma	6
Leiomyosarcoma	2
Epidermoid Ca.	2
Gastric adenocarcinoma	84
	—
	94

TABLE 7. *Elective Total Gastrectomy: Postoperative Complications*

	Males	Females	Total
Cardiac	14	10	24
Pulmonary	39	20	59
Wound	14	4	18
Anastamotic	12	7	19
None	9	2	11

the latter two undoubtedly primary esophageal cancers arising at the cardioesophageal junction but presenting clinically as gastric cancers. All of the remaining 84 patients had adenocarcinoma (Table 5).

At least one group of regional nodes contained metastatic cancer in 70 of the 94 patients, giving a 74.5% incidence of node metastasis.

In these 94 elective total gastrectomies the neoplasm occupied the proximal ⅓ of the stomach in 55 patients, the mid-⅓ of the stomach in 23 patients, and the distal ⅓ of the stomach in 16 patients (Table 6).

Postoperative-Complications

Cardiac complications occurred postoperatively in 24 patients. Six of the 14 male patients and 5 of the 10 female patients were known to have cardiac lesions preoperatively. The postoperative cardiac complications ranged from fibrillation to acute myocardial infarction with failure. Four deaths in these 94 patients were attributed primarily to cardiac complications: two patients died of cardiac decompensation, one patient died of acute myocardial infarction, and the fourth from a cerebral vascular accident.

Pulmonary Complications occurred in 59 patients. Some of these were undoubtedly influenced by the left thoracotomy, an integral part of the surgical procedure in most cases, including 24 instances of significant pleural effusion and 10 instances of persisting pneumothorax. Most of the pulmonary complications, however, were those of atelectasis (25 patients) and pneumonia (20 patients). The primary cause of death in one patient was staphylococcal pneumonia. Pneumonia was a contributing cause of death in 3 more patients.

Wound infection developed in 14 male and in 4 female patients. *Wound dehiscence* occurred in 2 male patients only.

Postoperative *thrombophlebitis* developed in 4 men and 1 woman, but was associated with sublethal pulmonary infarction in one male patient only.

Other complications were paralytic ileus in 5, jaundice associated with peritonitis in 5, parotitis in 2, renal failure in 2, and intestinal bleeding in one.

Eleven patients had uncomplicated postoperative courses (Table 7).

The most characteristic and troublesome complication in total gastrectomy is that of rupture of the esophago-enteric anastamosis. This occurred in 8 male and 6 female patients. There were 5 more patients with other anastamotic dehiscences. Seven of the 19 patients with anastamotic leaks succumbed. When this unfortunate complication occurred, our policy has always been to put the leaking anastamosis at rest, to treat the inevitable secondary infection aggressively, and to establish a distal feeding jejunostomy for nutritional support if and when feasible. In this manner 12 patients with leaking anastamoses were salvaged.

Results

Thirteen of the 64 male patients and 3 of the 30 female patients died as a result of the operative procedure and its complications. Postoperative deaths occurred from the third to the 170th postoperative day. An operative mortality rate of 17.0% for elective total gastrectomy is thus recorded.

Seventeen male and 5 female patients lived for more than 5 years, providing a 5-year salvage of 23.4%. Two male patients in this group subsequently died of gastric cancer at 68 months and 70 months following total gastrectomy, indicating an absolute 5-year cure rate of 21.2%. There have been no further deaths from gastric cancer in these survivors.

Thirteen male patients and 3 female patients have

TABLE 6. *Extended Total Gastrectomy: Location of Tumor*

	Males	Females	Total
Proximal 1/3	40	15	55
Middle 1/3	14	9	23
Distal 1/3	10	6	16
Total	64	30	94

TABLE 8. *Extended Total Gastrectomy: Microscopic Classification (Broders')*

	Males	Females	Total	
Not graded	7	2	9	10.7%
Grade I	1	0	1	1.2
Grade II	18	7	25	29.9
Grade III	24	11	35	41.7
Grade IV	11	3	14	16.6
Total	61	23	84*	100.1%

* Remaining 10 patients had lesions other than adenocarcinoma.

survived without recurrence or metastases for more than 10 years since definitive surgery, and provide a 10-year cure rate of 17.0%. The longest surviving patient is living with the infirmities of age 19½ years following extended total gastrectomy. Twenty-three patients have died apparently free of recurrence or metastases of gastric cancer. Several of these patients, obviously, lived free of cancer for many years, dying ultimately of the attrition of age or of other disease.

Forty-nine patients died of further manifestatations of gastric cancer from one month to 70 months following definitive surgery and only 7 of these 49 patients who ultimately died of gastric cancer lived for more than 3 years.

Discussion

It has been accepted that prognosis in gastric cancer is influenced by the size and gross characteristics of the neoplasm, by the degree of anaplasia of the lesion, and by the presence or absence of nodal metastases. The purpose of this analysis, however, is to determine the effectiveness of *elective* extended total gastrectomy for the control of gastric cancer as contrasted with conventional partial gastric resection irrespective of the size, gross characteristics, and microscopic appearance of the tumor. Actually, the Broders' classification of the tumors in 84 of these 94 patients is comparable to that which might be found in any random series of patients with gastric cancer (Table 8).

The initial thesis leading to the adoption of extended total gastrectomy for all resectable gastric cancers was based on demonstrable inadequacies of conventional gastrectomy. Extended total gastrectomy has been consistently performed by us for the past 20 years in the belief that a more adequate removal of the primary tumor and a more thorough dissection of regional lymph nodes has been accomplished thereby. If there were merit in the extended operation then some improvement in end results should have been accomplished merely as a result of the surgical procedure itself.

Despite this belief, we have demonstrated an absolute 5-year cure rate of only 21.2% and an apparent 10-year cure rate of only 17.0% in this series of 94 patients with gastric cancer subjected to elective total gastrectomy. During the preceding 20-year period, 1931–1950, there were 422 patients who were subjected to gastric resection with curative intent at Memorial Hospital, and a 5-year salvage of 21.6% was obtained in this group.[3] This figure is practically identical with that obtained by extended total gastrectomy in the ensuing 15 years. Furthermore, the operative mortality rate for the earlier 20-year period of 18.0% is comparable to that of 17.0% for the more recent series of patients undergoing elective total gastrectomy.

TABLE 9. *Gastric Carcinoma: 5-year Salvage (Memorial Hospital, NYC)*

	Partial gastrectomy 1931–1950	Extended Total gastrectomy 1950–1964
Proximal 1/3	19.0%	12.7%
Middle 1/3	33.5	34.8
Distal 1/3	29.8	43.7
Total	21.6%	21.2%

It is certain that criteria of resectability have been extended. Undoubtedly some of the patients treated by extended total gastrectomy in recent years would have been adjudged non-resectable in earlier years. Many of the lesions in the proximal gastric segment, treated by total gastrectomy during the period under study, were routinely considered inoperable in the earlier period.

It is therefore of interest to note that more than half of the elective total gastrectomies were performed for lesions of the proximal ⅓ of the stomach (Table 6). Twenty-three patients had cancers of the mid-⅓ of the stomach and, 16 patients had cancers of the distal ⅓ of the stomach. Only 7 of the 55 patients with proximal gastric lesions survived for 5 or more years free of cancer (12.7%). Eight of the 23 patients with mid gastric lesions survived for 5 or more years free of cancer (34.8%), and 7 of the 16 patients with distal gastric lesions survived for 5 or more years free of cancer (43.7%). Comparative figures for the preceding 20 years (1931–1950) in the practice of Memorial Hospital are as follows: in 337 patients surviving curative resection there was a 19.0% 5-year salvage for lesions of the proximal ⅓ of the stomach, 33.5% 5-year salvage for lesions of the mid ⅓, and 29.8% 5-year salvage for lesions of the distal ⅓ (Table 9).

In the 7 surviving patients of the 55 with proximal lesions treated by extended total gastrectomy only 3 had positive lymph node metastases, one of whom had a primary lymphosarcoma of the stomach with metastases to 2 node areas. Because of the tendency of cancers in the proximal segment to extend into the esophagus and to metastasize to mediastinal lymphatics, it is probable that extended total gastrectomy, as heretofore

TABLE 10. *Gastric Carcinoma: 5-year Survivors (Incidence of Nodal Metastasis)*

	Partial Gastrectomy 1931–1950		Extended Total Gastrectomy 1950–1964		
Proximal 1/3	3/10	30%	3/7		43%
Middle 1/3			5/8		
	14/55	25.5%		11/15	73%
Distal 1/3			6/7		

described, can offer little more than can be obtained by proximal gastrectomy, and that early lesions without node metastases could be treated successfully either by partial gastrectomy or by total gastrectomy. We hold certain reservations about the desirability of esophagogastric reconstruction as compared to esophagojejunal reconstruction, but these are not pertinent to the present discussion.

In the smaller number of patients with cancers of the mid ⅓ or distal ⅓ of the stomach treated by extended total gastrectomy, however, most of the 5-year survivors had nodal metastases. Five of the 8 surviving patients with cancer of the mid ⅓ of the stomach, and 6 of the 7 surviving patients with cancer of the distal ⅓ of the stomach had such nodal metastases (11 of 15 patients, or 73%), contrasted with only 14 patients with positive nodes in 55 surviving patients treated by partial gastrectomy in the earlier Memorial Hospital series (14 of 55 patients, or 25.5%) (Table 10).

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Letters to the Editor

Dear Editor:

Work published in this journal in September 1971 indicated that the net contribution of elective or so-called "prophylactic" regional lymph node dissection to the treatment of patients with primary malignant melanoma was slight, if not negligible.[6] Indeed, the harm from the regular practice of elective lymphadenectomy was almost as great as its benefits. However, assuming there must be a place for elective lymphadenectomy in the treatment of malignant melanoma, we attempted to identify a subset of these patients who truly would benefit significantly from the regular practice of elective regional node dissection associated with adequate local excision of the primary melanoma. We attempted to predict the likelihood of clinically occult regional lymph node metastases according to certain patient characteristics: age, sex, coexisting disease, greatest diameter of the primary melanoma, depth of invasion and degree of cellular aggressiveness. We were unable to identify prospectively such individuals. We then turned our attention to predicting survival or non-survival in these patients, reasoning that those patients whose prognosis after local excision alone was extremely good should have only that treatment, and those patients who had poor prognoses should be considered reasonable candidates for elective lymphadenectomy for *possible* improvement of their prognoses.

Discriminant function analysis of the six variables noted above allowed development of a set of coefficients which was 95% accurate in predicting life or death from melanoma in the patient population studied at the University of Miami School of Medicine. We concluded that one might apply this formula to such variables and identify patients who were more likely than the whole population of primary melanoma victims to benefit from routine elective regional node dissection.

The main purpose of this brief report is to reaffirm our conclusions on the negligible contribution of elective lymphadenectomy in malignant melanoma to the overall salvage rate of patients seen with clinical Stage I disease. The secondary purpose of this report is to describe the failure of the coefficients generated by discriminant function analysis in Miami to predict accurately the likelihood of lymph node metastases when applied to a patient population studied in Louisville, Kentucky.

Specifically, the discriminant function weighting characteristics were applied to all patients treated with clinical Stage I melanoma at Louisville General Hospital from 1948 to 1970. In many demographic and clinical respects, the population was very different from that seen in Miami. When applied on a similar basis to patient data from Louisville, the weighting coefficients were not predictive of survival. A limited attempt to apply the discriminant function coefficients retrospectively to patient data accumulated from the Queensland Melanoma Project likewise met with failure.[5] New coefficients allowed accurate prediction for the Louisville population but were not applicable to the Miami experience.

The international consensus regarding malignant melanoma manifests a strong and growing conviction that elective or prophylactic regional node dissections are of very limited value in the treatment of patients with primary clinical Stage I melanoma.[3,7] A number of centers with great experience and skill in the evaluation of melanoma have attempted to develop schemes to predict outcome according to various prognostic factors; each of these has been impressive, and often statistically valid, with respect to the patients in the institution where the scheme was formulated.[1,2,4] However, the schemes have, by and large, failed to predict prognoses broadly enough to be useful elsewhere. Some modification of the factors considered in our discriminant function analysis, as well as those suggested by others or their products, may prove helpful as to the presently elusive factors which indicate probable outcome in clinical Stage I malignant melanoma.

Indeed, we continue our efforts to modify this concept, feeling that there must be a subset of patients who would genuinely benefit from elective adjunctive therapy, given adequate primary treatment by local excision of the melanoma. This communication has described our failure to identify such a group to date. It has also redefined the weighting coefficients previously reported as approximations that are unsuitable for direct application to other patient populations afflicted with primary intact malignant melanoma with clinically normal regional lymph nodes.

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Dear Editor:

In their excellent paper "Patho-physiological Changes Following Ischemia of the Spleen" (Ann. Surg., **178**:179, 1973) Tsapogas *et al.* carried out experiments in dogs to determine if ischemia of the spleen, due to partial or total interruption of its blood supply, makes splenectomy mandatory. They make the statement that splenectomy routinely follows the use of the splenic artery for revascularization of abdominal viscera.

Encouraged by the report by Blain and Blain from 1950 on "Ligation of the Splenic Artery in Portal Hypertension and Banti's Syndrome," I have preferred not to remove the spleen in the three cases in whom I have used the splenic artery for revascularization. In one case the patient suffered from renal artery stenosis, in one case from renal artery occlusion, and in the third case from an aortic aneurysm extending above the renal arteries. The ligation of the splenic artery did not seem to have any harmful effect in any of these patients. The platelet count or red cell count did not seem to be influenced by the splenic artery interruption. One patient died two months postoperatively from a bleeding duodenal ulcer. No macro- or microscopical abnormalities were found in the spleen on post-mortem examination.

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Professor of Surgery
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214 01 Malmö, Sweden

Dear Editor:

Thank you very much for giving us the opportunity to read and respond to Professor Bergentz's comments on our article.

We appreciated the complimentary remarks on our study. As shown in our experimental work, splenic artery ligation does not result in significant changes in the hematological picture and the histological structure of the spleen. However, when complete dearterialization was performed by ligating the main splenic artery, the short gastric and other attachments to the spleen, profound histological changes did occur to this organ.

Since 1960 we too, among others, occasionally utilized the splenic artery for revascularization of neighboring stenosed visceral arteries, only when established reconstructive arterial procedures were not feasible. The spleen was left *in situ* and care was taken during the dissection not to unduly disturb the short gastric and the other smaller vessels to the spleen. As Professor Bergentz reports, we too had no overt side effects in those instances. It is, however, important to note that in the rare instances when the splenic artery is considered to be used as a graft, careful assessment of its caliber is an essential prerequisite. We found the splenic artery significantly stenosed, usually due to atheroma, in about one-third of the cases.

Makis J. Tsapogas, M.D., M.Chir., F.A.C.S.
Department of Surgery
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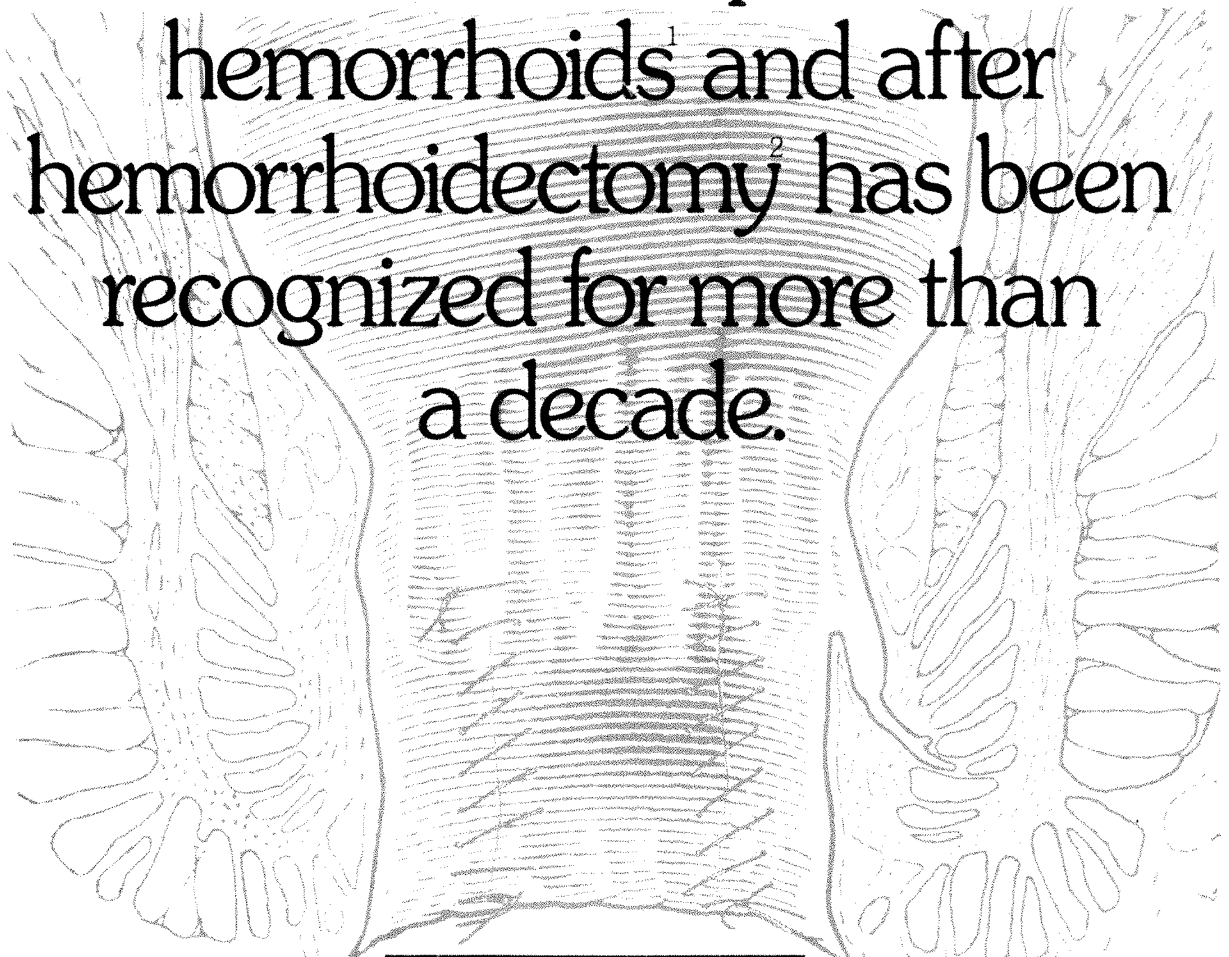

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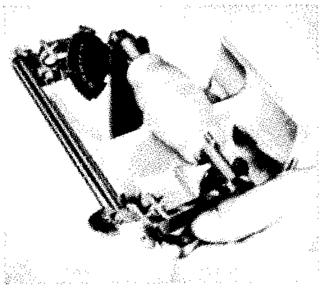

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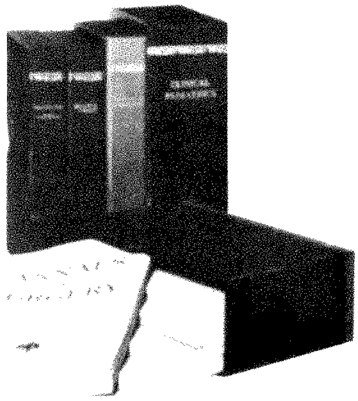

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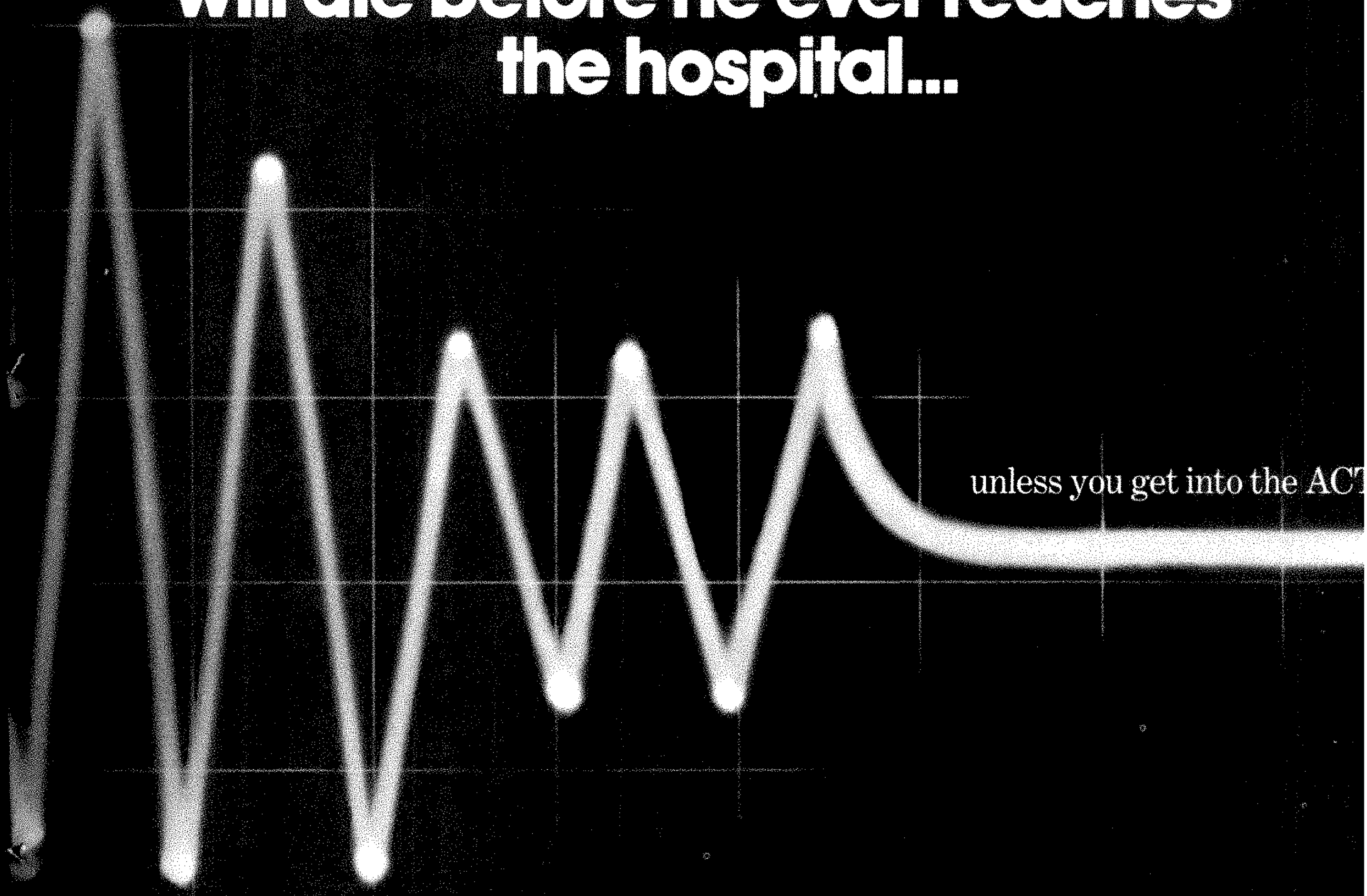

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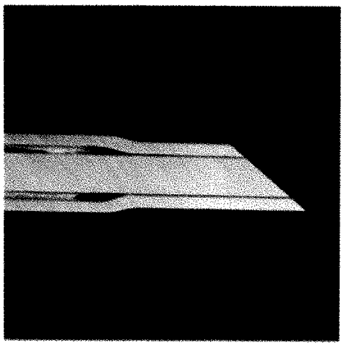

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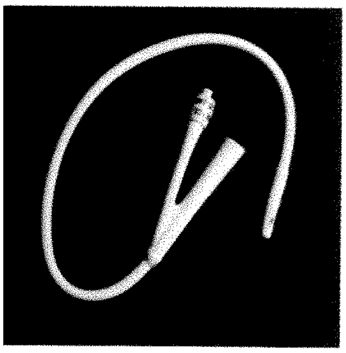

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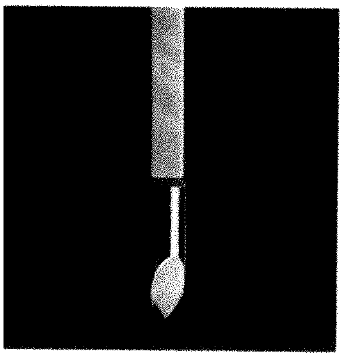

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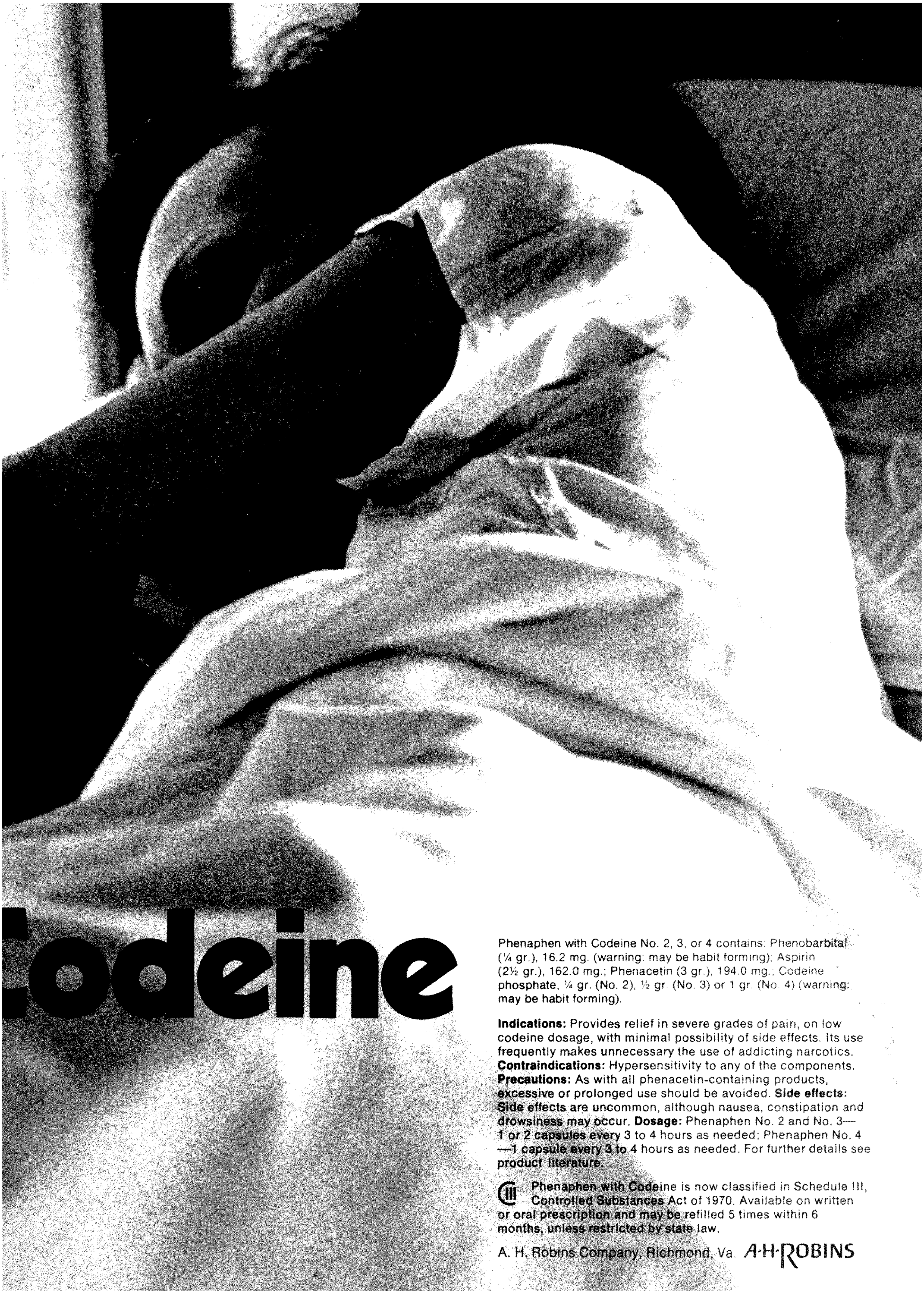

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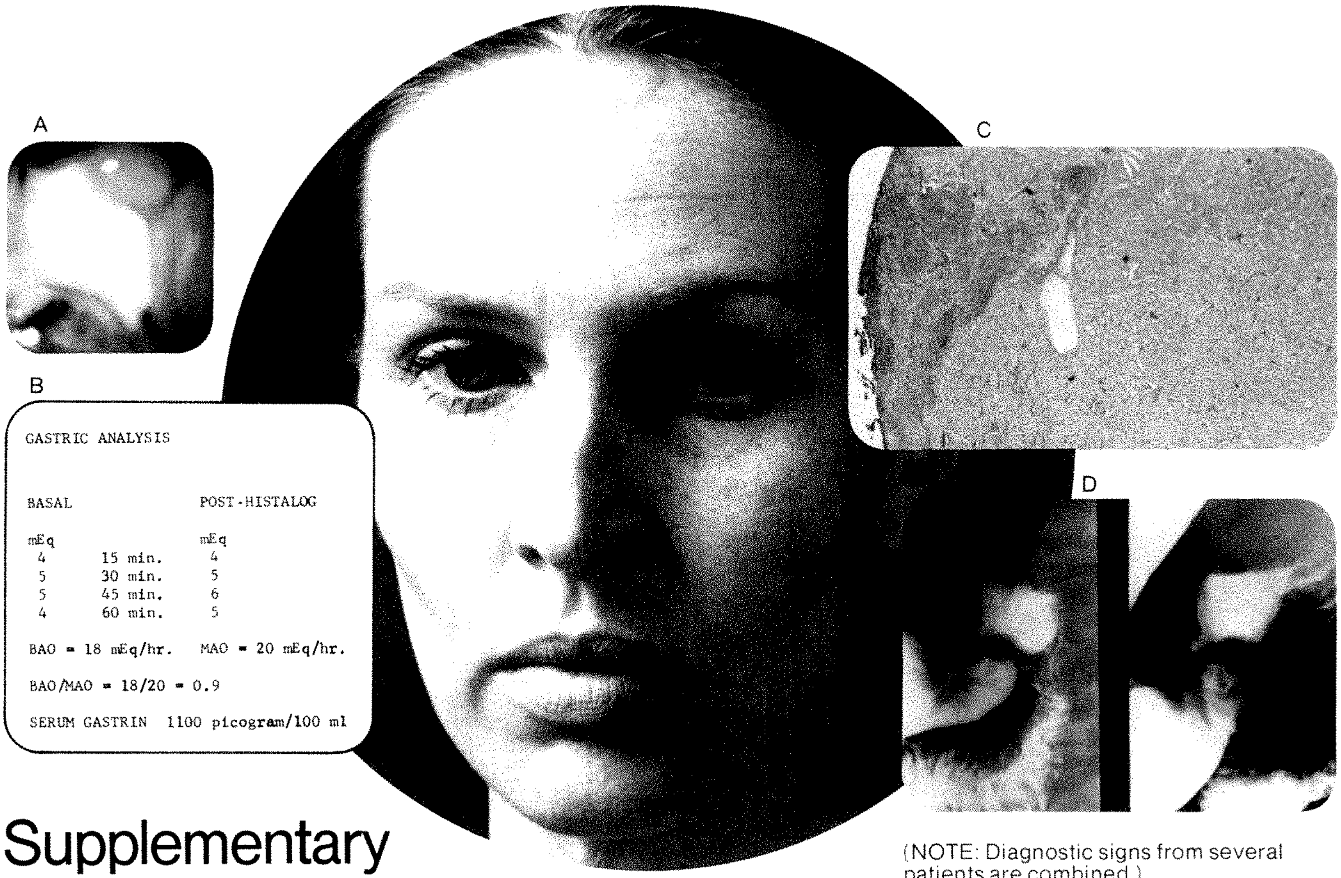

GASTRIC ANALYSIS

BASAL		POST-HISTALOG
mEq		mEq
4	15 min.	4
5	30 min.	5
5	45 min.	6
4	60 min.	5

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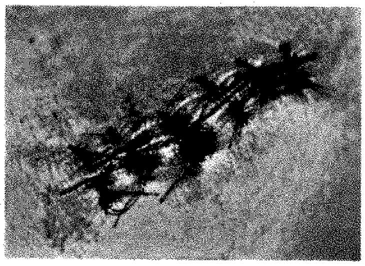

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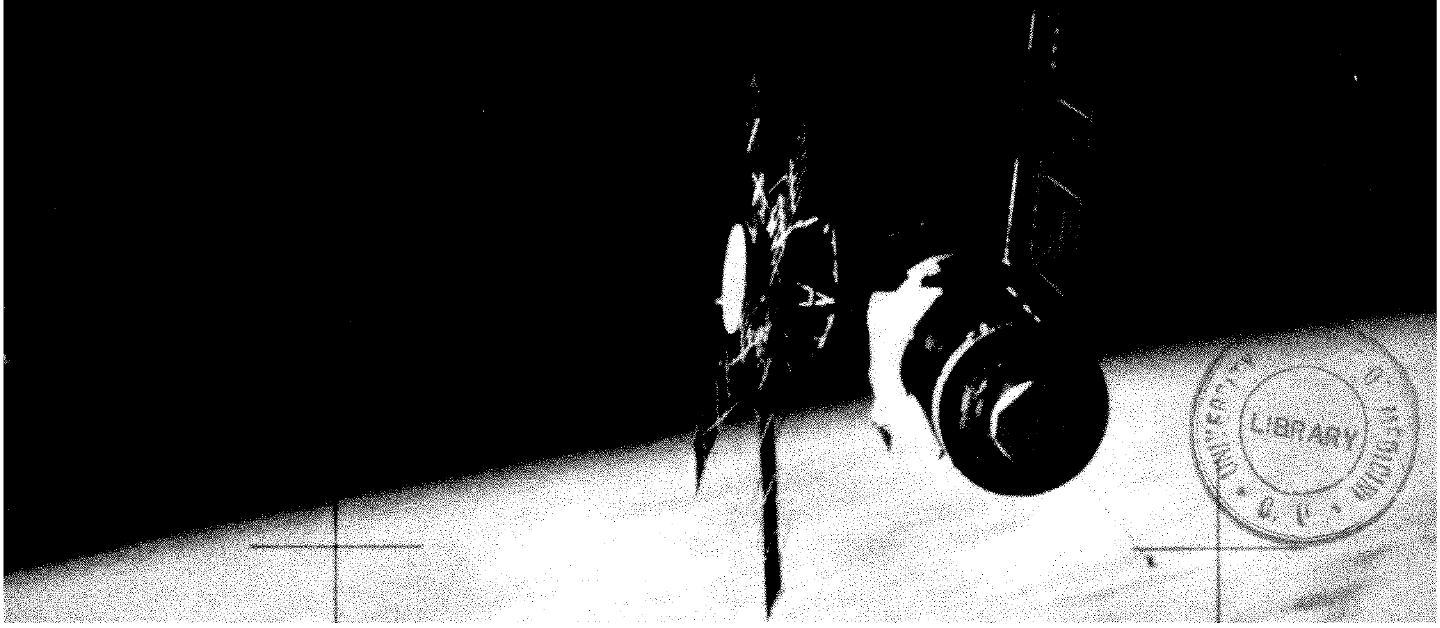

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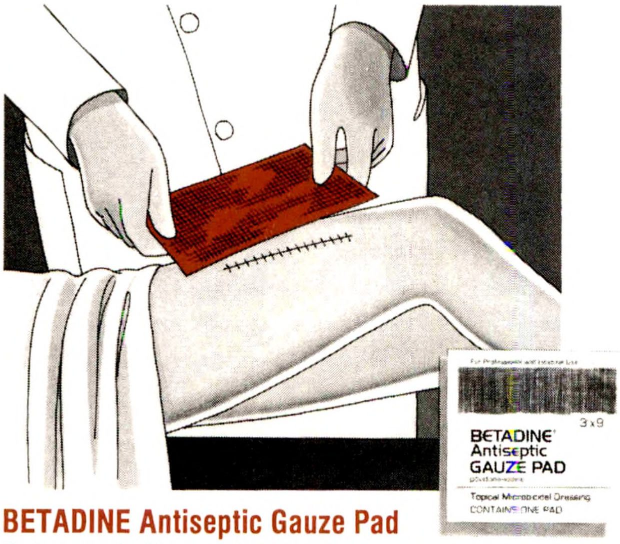

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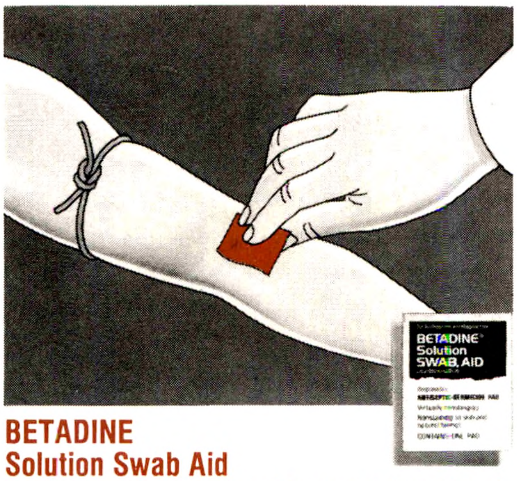

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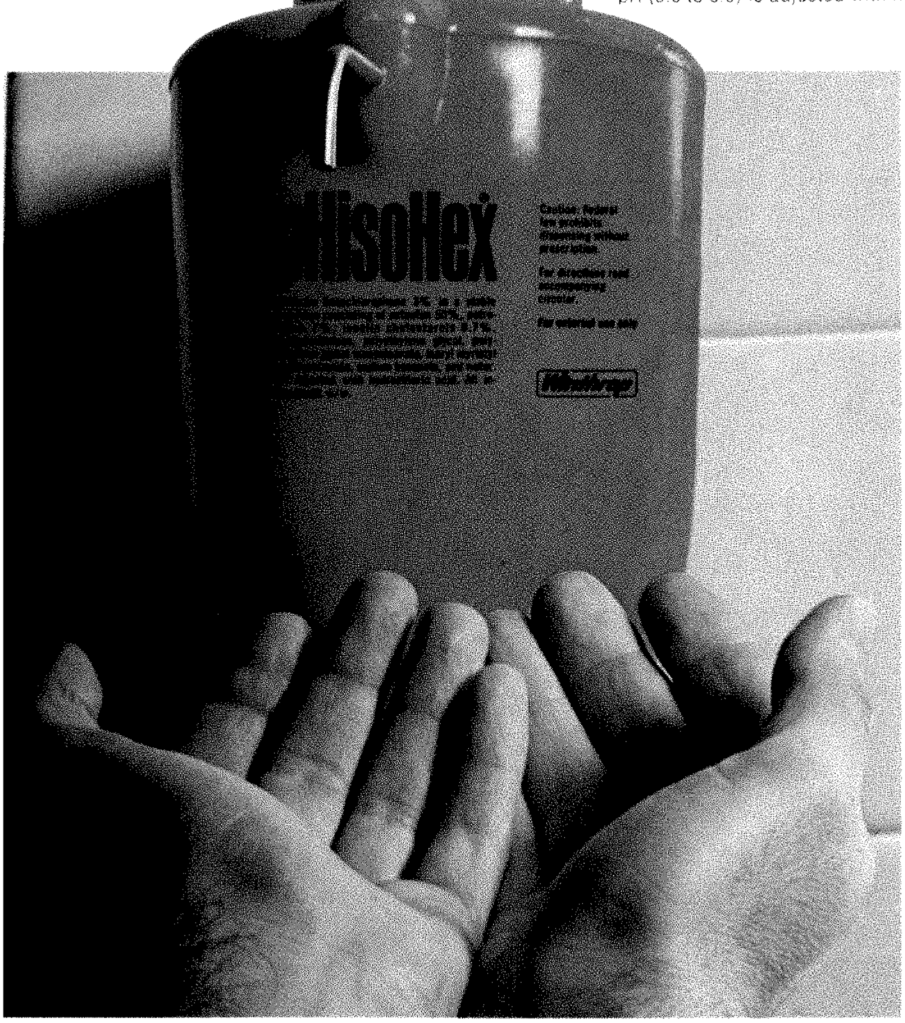

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Actions: pHisoHex has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control. (See Warnings.)

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: RINSE THOROUGHLY AFTEh USE, especially from sensitive areas such as the scrotum and

dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions. Vacuolization has been reported, with a symmetrical, rostrocaudal distribution in the brainstem reticular formation of premature infants of low birth weight, especially those with skin rashes and wounds, who were washed with 3% hexachlorophene. However, the clinical correlates of such vacuolization have not been established since these infants also had critical clinical conditions or pathologic findings of independent etiology. Some recent opinions express particular concern with respect to the use of pHisoHex on premature infants. Although the scientific picture is still incomplete, pHisoHex should not be used on premature infants unless, in the judgment of the prescribing physician, its use is required by the unique circumstances of an individual case.

When preparations containing hexachlorophene are left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms.

PHISOHEX SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin, or exposure to a powder accidentally containing approximately 6.5% hexachlorophene.

Examinations of brain tissue in some of these cases revealed vacuolization like that which can be pro-

pHisoHex is intended for *external use only.* If swallowed, pHisoHex is harmful, especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precaution: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, plastic bottles of 1 gallon, and ¼ oz. (8 ml.) unit packets, boxes of 50. pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts.

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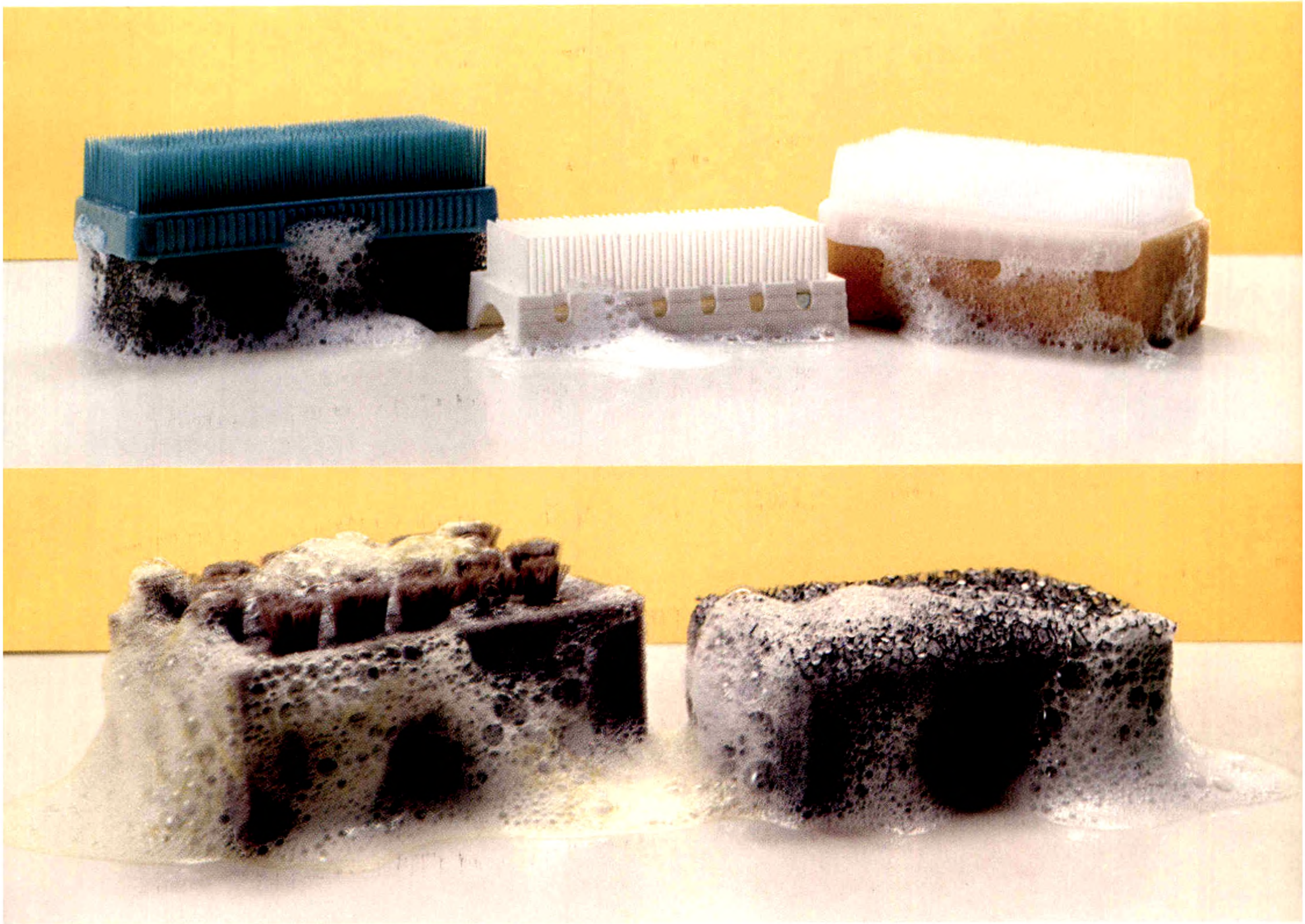

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McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg., **174**:58, 1971.

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- Genitourinary tract infections due to *E. coli, P. mirabilis*, Klebsiella spp. or *Staphylococcus aureus*, including penicillin G-resistant staph.

Low incidence of venous irritation on I.V. administration... well tolerated locally

In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low. *Controlled studies* in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly.

Cephalosporins are reported to produce maculopapular rash, urticaria, reactions resembling serum-sickness and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

In penicillin-allergic patients, cephalosporins should be used with great caution. There is clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins, and there are instances of patients who have had reactions to both drugs (including fatal anaphylaxis after parenteral use).

Flexible Dosage: adjustable to fit severity of infection and renal status of patient:

The usual adult dose of Cefadyl is 0.5 Gm. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. Doses up to 12 Gm. daily may be used in very serious or life-threatening infections.

No nephrotoxicity reported during extensive clinical trials

In fact, when Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported. However, renal status of patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate. Rises in BUN have been observed; their frequency increases in patients over 50 years old. (See Dosage, Adults—in Prescribing Information on last page.)

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CEFADYL® (sterile cephapirin sodium)
7628 DIRO-04 March, 1974

Description. Cefadyl (sterile cephapirin sodium) is a cephalosporin antibiotic intended for intramuscular and intravenous administration only. It is supplied as the sodium salt of 7-[α-(4-pyridylthio)-acetamido]-cephalosporanic acid. Each 500 mg. contains 1.07 milliequivalents of sodium.

Actions. *Human Pharmacology*—Following intramuscular administration of single 500 mg. and 1 Gm. doses to normal volunteers, average peak serum levels of 9.0 and 16.4 mcg./ml. respectively, were attained at 30 minutes, declining to 0.7 and 1.0 mcg./ml. respectively, at 4 hours and 0.2 and 0.3 mcg./ml. respectively, at 6 hours.

Cefadyl and its metabolites were excreted primarily by the kidneys. Antibiotic activity in the urine was equivalent to 35% of a 500 mg. dose 6 hours after I.M. injection and to 65% of a 500 mg. dose 12 hours after injection. Following an I.M. dose of 500 mg., peak urine levels averaged 900 mcg./ml. within the first 6 hours.

Following rapid intravenous administration of single 0.5 Gm., 1 Gm., and 2 Gm. doses, peak serum levels of 35, 67 and 129 mcg./ml. respectively, were attained at 5 minutes, declining to 6.7, 14.0 and 31.7 mcg./ml. respectively, at 30 minutes and 0.27, 0.61 and 1.11 mcg./ml. respectively, at 3 hours.

Seventy percent of the administered dose was recovered in the urine within 6 hours. Repetitive intravenous administration of 1 Gm. doses over 6-hour periods produced serum levels between 4.5 and 5.5 mcg./ml.

44 to 50% of Cefadyl is bound to human serum. The average serum half-life of Cefadyl in patients with normal renal function is approximately 36 minutes.

The major metabolite of cephapirin is desacetyl cephapirin which has been shown to contribute to antibacterial activity.

Controlled studies in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly. In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low.

Microbiology—*In vitro* tests demonstrate that the action of cephalosporins results from inhibition of cell-wall synthesis. Cefadyl is active against the following organisms *in vitro*:

Beta-hemolytic streptococci and other streptococci. (Many strains of enterococci, e.g., *S. faecalis,* are relatively resistant.)

Staphylococci, including coagulase-positive, coagulase-negative, penicillinase and non-penicillinase producing strains. *Diplococcus pneumoniae, Haemophilus influenzae, Proteus mirabilis, Escherichia coli,* Klebsiella species.

Most strains of enterobacter and indole-positive Proteus *(P. vulgaris, P. morganii, P. rettgeri)* are resistant to Cefadyl. Methicillin-resistant staphylococci, Serratia, Pseudomonas, Mima and Herellea species are almost uniformly resistant to Cefadyl.

Disc Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to cephalosporin class antibiotics. Interpretations correlate diameters of the disc test with MIC values for Cefadyl. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Indications. Cefadyl is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Group A beta-hemolytic streptococci: Skin and soft tissue infections. Respiratory infections.

(Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefadyl is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cefadyl in the subsequent prevention of rheumatic fever are not available at present.)

Staphylococcus aureus (penicillinase producing and non-penicillinase producing): Skin and soft tissue infections. Urinary tract infections.

Diplococcus pneumoniae: Respiratory tract infections.

Haemophilus influenzae: Respiratory tract infections.

Escherichia coli: Urinary tract infections, skin and soft tissue infections and bacteremia.

Klebsiella species: Urinary tract and respiratory tract infections.

Proteus mirabilis: Urinary tract infections.

Note: Appropriate bacteriological studies should be performed to identify the causative organisms and determine its susceptibility. Therapy may be started while awaiting results of these studies.

Contraindications. Cefadyl (sterile cephapirin sodium) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings. IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exceptions should be made with regard to Cefadyl.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions. The renal status of the patients should be determined prior to and during Cefadyl (sterile cephapirin sodium) therapy, since in patients with impaired renal function, a reduced dose may be appropriate (see *Dosage, Adults*). When Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported.

Prolonged use of Cefadyl may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Adverse Reactions. *Hypersensitivity*—Cephalosporins were reported to produce the following reactions: maculopapular rash, urticaria, reactions resembling serum-sickness, and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—During large scale clinical trials, rare instances of neutropenia, leukopenia, anemia were reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs test during therapy with other cephalosporins.

Liver—Elevations in SGPT or SGOT, alkaline phosphatase, and bilirubin have been reported.

Kidney—Rises in BUN have been observed; their frequency increases in patients over 50 years old.

Dosage. *Adults*—The usual dose is 500 mg. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. The lower dose of 500 mg. is adequate for certain infections, such as skin and soft tissue and most urinary tract infections. However, the higher dose is recommended for more serious infections.

Very serious or life-threatening infections may require doses up to 12 Grams daily. The intravenous route is preferable when high doses are indicated.

Depending upon the causative organism and the severity of infection, patients with reduced renal function (moderately severe oliguria or serum creatinine above 5.0 mg./100 ml.) may be treated adequately with a lower dose, 7.5 to 15 mg./Kg. of cephapirin every 12 hours. Patients with severely reduced renal function and who are to be dialyzed should receive the same dose just prior to dialysis and every 12 hours thereafter.

Children—The dosage is in accordance with age, weight and severity of infection. The recommended total daily dose is 40 to 80 mg./Kg. (20 to 40 mg./lb.) administered in four equally divided doses.

The drug has not been extensively studied in infants; therefore, in the treatment of children under the age of three months the relative benefit/risk should be considered.

Therapy in beta-hemolytic streptococcal infections should continue for at least 10 days.

Where indicated, surgical procedures should be performed in conjunction with antibiotic therapy.

Administration. Cefadyl may be administered by the intramuscular or the intravenous routes.

Intramuscular Injection—The 1 Gm. vial should be reconstituted with 2 ml. of Sterile Water for Injection, U.S.P. Each 1.2 ml. contains 500 mg. of cephapirin. All injections should be deep in the muscle mass.

Intravenous Injection—The intravenous route may be preferable for patients with bacteremia, septicemia, or other severe or life-threatening infections who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending. If patient has impaired renal function, a reduced dose may be indicated (see *Dosage, Adults*). In conditions such as septicemia, 6 to 8 Gm. per day may be given intravenously for several days at the beginning of therapy; then, depending on the clinical response and laboratory findings, the dosage may gradually be reduced.

When the infection has been refractory to previous forms of treatment and multiple sites have been involved, daily doses up to 12 Gm. have been used.

Intermittent Intravenous Injection—The contents of the 1 Gm. vial should be diluted with 10 ml. or more of diluent and administered slowly over a 3 to 5 minute period or may be given with intravenous infusions.

Intermittent Intravenous Infusion with Y-Tube—Intermittent intravenous infusion with a Y-type administration set can also be accomplished while bulk intravenous solutions are being infused. However, during infusion of the solution containing Cefadyl (sterile cephapirin sodium), it is desirable to discontinue the other solution. When this technique is employed, careful attention should be paid to the volume of the solution containing Cefadyl so that the calculated dose will be infused.

Continuous Intravenous Infusion—After reconstitution, Cefadyl may be added to the solutions listed below under *Stability*. The choice of solution and volume should be dictated by the fluid and electrolyte management of the patient.

Stability. *Storage Stability*—After reconstitution, Cefadyl is stable for 12 hours at room temperature and 10 days under refrigeration when reconstituted with Sterile Water for Injection, U.S.P. The pH of the resultant solution ranges from 6.5 to 8.5. During these storage conditions, no precipitation occurs. A change in solution color during this storage time does not affect the potency.

Compatibility with the Infusion Solutions: Cefadyl is stable and compatible for 24 hours at room temperature at concentrations between 2 mg./ml. and 30 mg./ml. in the following solutions:

Sodium Chloride Injection, U.S.P., 5% W/V Dextrose in Water, U.S.P., Sodium Lactate Injection, U.S.P., 5% Dextrose in Normal Saline, U.S.P., 10% Invert Sugar in Normal Saline, 10% Invert Sugar in Water, 5% Dextrose +0.2% Sodium Chloride Injection, U.S.P., Lactated Ringer's with 5% Dextrose, 5% Dextrose + 0.45% Sodium Chloride Injection, U.S.P., Ringer's Injection, U.S.P., Lactated Ringer's Injection, U.S.P., 10% Dextrose Injection, U.S.P.

Supply. Cefadyl (sterile cephapirin sodium) for I.M. or I.V. injection. Cephapirin sodium equivalent to 1 Gm. cephapirin. **NDC** 0015-7628-1-Gm. vial.

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*Bauer, A.W., Kirby, W.M.M., Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol., 45:493, 1966. Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972.

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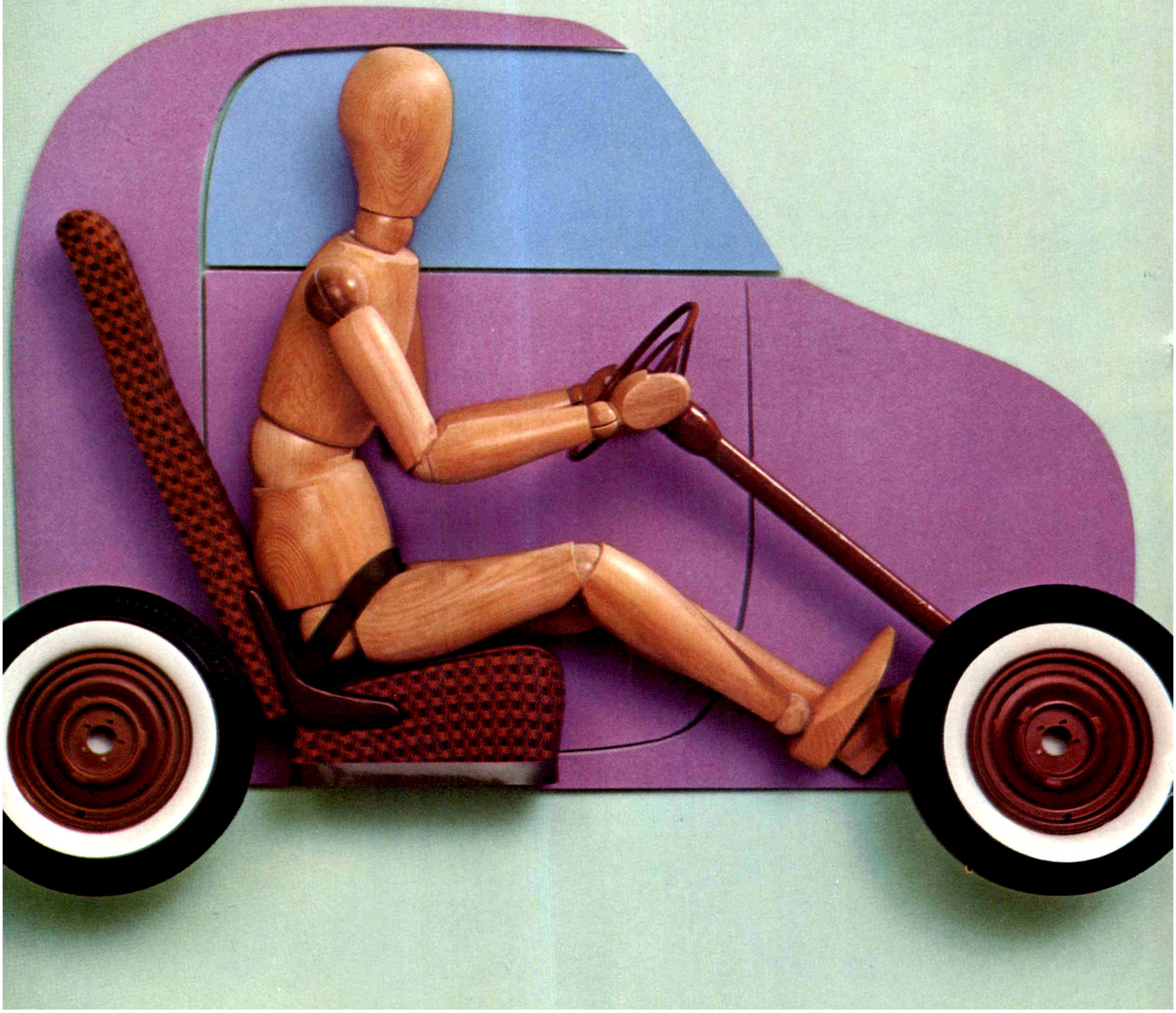

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ANNALS OF SURGERY

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A Followup Report of a Prospective Evaluation of Vagotomy-Pyloroplasty and Vagotomy-Antrectomy for Treatment of Duodenal Ulcer

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A prospective randomized study of 200 consecutive patients who required elective operation for treatment of duodenal ulcer was conducted. Truncal vagotomy and drainage (V-D) was done in 108 patients with a 2% mortality and truncal vagotomy and antrectomy (V-R) were performed in 92 patients with no mortality. Ninety-four per cent of these patients were followed 5–8 years after operation or until their death if that preceded the termination of the study. The immediate postoperative morbidity including stomal dysfunction and reoperation was greater after V-D than after V-R. In the opinion of the patients and independent investigators, the number of gastrointestinal complaints was similar throughout the study for the two groups of patients. In the opinion of the author, however, more gastrointestinal complaints occurred in patients from the V-R group than from the V-D group. Because of the subjectivity involved in the evaluation of these complaints, it is unknown whether a real difference existed between the two groups of patients. No patient in either group was symptomatically disabled after operation. There were nine recurrent ulcers requiring reoperation after V-D and one after V-R. The insulin test was positive in 58% of patients after V-D and 14% after V-R. These figures were essentially unchanged from those in the first report made three to five years after operation. The basal acid output and the response to histalog stimulation also remained unchanged in the two groups of patients during the same period. This study suggests that if one abstains from resection in patients where technical difficulties with the duodenum can be expected, V-R can be performed in the remaining patients with a mortality rate equally as low as that usually reported for V-D. It is concluded that V-R is superior to V-D for the majority of patients because it is associated with fewer recurrent ulcers without a significant difference in the severity of other postoperative gastrointestinal complaints.

A PROSPECTIVE STUDY was begun in November, 1964 to compare the results of vagotomy and pyloroplasty (V-P) with vagotomy, antrectomy and Billroth I(V-BI) in the treatment of patients undergoing elective operation for duodenal ulcer. Two hundred consecutive patients accrued to the study between that time and October, 1967. When the three to five year followup results of this study were presented,[5] we concluded that V-BI can be performed as safely as V-P if one abstains from performing the operation in patients where technical difficulties with the duodenal stump can be anticipated. V-BI was considered superior to V-P because it was associated with a significantly lower recurrence rate than occurred after V-P without there being a significant difference between the two operations in the frequency of gastrointestinal symptoms. The present report extends the period of follow-up evaluation so that the majority of these patients have now been studied five to eight years after operation.

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TABLE 1. *Length of Time Patients Were Studied Postoperatively*

Time Followed	No. of Patients V-D	No. of Patients V-R
5 to 8 Years	86	80
4 to 4.5 Years	3	7 (4)
Less than 4 Years	19 (14)	5 (4)
Total	108	92

1. ( ) = Followed until death.
2. % of patients followed for duration of study or until death. $\frac{188}{200} = 94\%$
3. % of patients followed for duration of study that were followed in person. $\frac{170}{188} = 90\%$
4. % of patients lost or dead with no followup. $\frac{6}{200} = 3\%$

Clinical Material

In the original randomization, 98 patients were assigned to V-P and 102 to V-BI. The surgeons were permitted the options of substituting gastroenterostomy (V-GE) for pyloroplasty and Billroth II (V-BII) for Billroth I anastomosis if in their opinion the pathology involving the duodenum was too hazardous to permit the operation indicated by the protocol. In addition to these two options, the protocol was violated in ten patients and a drainage operation was performed because resection was considered too dangerous. Thus the operations actually performed were V-P in 94, V-GE in 14, V-BI in 73 and V-BII in 19 patients. As in the original presentation, these patients are to be considered in two groups, vagotomy-drainage (V-D) 108 and vagotomy-resection (V-R) 92. Every effort was made to follow these patients by readmitting them to the hospital at yearly intervals. Secretory studies were performed under the same rigid conditions and by the same personnel as were those previously reported. They included an augmented histalog test, an insulin test and a two hour basal secretory study before each test. Attempts were made by telephone or written questionnaire to follow patients who failed to return to the hospital. The success of the followup attempts is shown in Table 1. Ninety-four per cent of patients were followed for the duration of the study or until their death and in 90% of these patients the final followups were made in person. A followup was completely lacking in six patients because of death or failure of the patient to return. All patients who were classified as having been followed for the duration of the study were not necessarily seen or interviewed at each intervening year during the study. Thirty-two patients died while the study was in progress. This included the two operative deaths; both occurred after V-P. One was the result of a pulmonary embolus and the other was due to hepatitis and a duodenal fistula. None of the 30 late deaths occurred as a consequence of duodenal ulcer disease or of the operation.

Late Clinical Results

The gastrointestinal complaints that were acknowledged by the patients are tabulated in Table 2. The frequency of symptoms recorded in the first study at three years are given for comparison. The number of symptoms at three years was about equally divided between the patients in the V-R group and in the V-D group with a slight advantage in favor of the V-D group. After five to eight years the number of symptoms had decreased in both groups but the reduction was greater in the V-D group than it was in the V-R group. The majority of the complaints occurred only occasionally and were not of serious magnitude. In addition, it was frequently impossible to determine whether the symptoms were related to the operation that had been performed or whether they were incidental to dietary indiscretions, alcoholic overindulgence or some other cause. In the original report hiatus hernia was diagnosed in 18 patients after V-R and in 14 patients after V-D. Three patients in each group were operated upon for this condition. Symp-

TABLE 2. *Frequency of Postoperative Gastrointestinal Symptoms*

Number of Years Patients Were Studied	V-D 5 to 8	V-D 4 to 4.5	V-D Less than 4	V-D First Study at 3 Years	V-R 5 to 8	V-R 4 to 4.5	V-R Less than 4	V-R First Study at 3 Years
Patients studied	86	3	14	84	80	7	4	77
	Patients with Symptoms				Patients with Symptoms			
Pain	4	0	0	8	6	0	1	10
Dysphagia	3	0	1	10	8	1	0	8
Early fullness	7	0	2	12	10	1	1	18
Nausea	6	0	1	12	15	2	2	15
Vomiting	5	0	1	9	13	1	2	17
Abdominal cramps	2	0	1	10	10	1	2	8
Sweating	11	0	2	18	18	2	1	26
Palpitation	10	0	1	18	18	3	0	15
Weakness	11	0	2	18	23	2	2	26
Need to lie down after eating	8	0	1	18	17	0	2	18

TABLE 3. *Change in Weight One to Eight Years After Operation*

V-D			V-R		
Weight of Patients			Weight of Patients		
Pre op.	Post op.		Pre op.	Post op.	
	Under	3		Under	4
Under 9	Normal	3	Under 7	Normal	3
	Over	3		Over	0
	Under	5		Under	6
Normal 52	Normal	42	Normal 54	Normal	43
	Over	5		Over	5
	Under	0		Under	0
Over 43	Normal	14	Over 27	Normal	10
	Over	29		Over	17

Pre- and postoperative weights are based on Metropolitan Life Insurance table of ideal weights.

toms of reflux and evidence for a hiatus hernia persisted in ten patients from each group. Dysphagia was a minor problem and was more prevalent in the V-R patients than in the V-D patients. Undoubtedly some of the hiatal hernias and their related symptomatology were the consequence of the dissection required for truncal vagotomy. In our opinion the problem of dysphagia after truncal vagotomy was accentuated by the reduction in the stomach's storage capacity following resection.

Some combination of vasomotor symptoms occurred in 21 patients who had V-R and in 15 patients who had V-D. These symptoms were almost equally divided between those related to early and late dumping. Early dumping was not debilitating for any patient and was considered of consequence in only one patient after V-D and two patients after V-R. Late dumping was easily controlled in each patient with this problem.

The ideal weight of patients was based on those published by the Metropolitan Life Insurance Company. Patients were considered underweight if they weighed less than 90% of their ideal weight; normal if their weight was within plus or minus 10% of ideal weight and overweight if they weighed more than 10% above the ideal weight. The results of operation upon the patient's weight are seen in Table 3. After V-D and V-R 5% and 6% of patients, respectively, were underweight at the time of the first report. At the termination of the study 8% and 11% of patients in these categories were underweight. This did not represent a significant difference between the two groups of patients with respect to maintenance of their weight, nor was there in either group an important difference between the preoperative and postoperative weights.

Diarrhea was recorded in 19 patients after V-D and 11 patients after V-R. In most of these patients diarrhea was of no more consequence than it is in patients who have had no gastrointestinal surgery. Again diarrhea was arbitrarily defined as significant either if an attack occurred once a week, lasted two or more days and consisted of three or more stools per day or if the patient had explosive diarrhea which resulted in soiling. Using these criteria, significant diarrhea occurred in ten patients equally divided between the V-D and V-R groups. This represented no change in distribution of patients but the number with diarrhea was smaller than that in the first report.

At the time of the first report, eight patients with V-D and none with V-R had been reoperated for recurrent ulcer. Those patients who were reoperated have had no additional symptoms of recurrence. Since the last report one additional patient has had an antrectomy and BI anastomosis for recurrent ulcer three years after V-P. He has remained well for three years since operation and his insulin test which had been positive became negative even though further vagotomy was not performed. Another patient developed obstruction due to a marginal ulcer five years after V-BI. He required re-resection and has been without symptoms of recurrence for three years since his second operation. Thus there have been nine recurrent ulcers after V-D for an incidence of 8.3% and one recurrent ulcer after V-R for an incidence of 1.1%. The three patients who were suspected previously of having a recurrent ulcer were followed closely and have had no further evidence of recurrence. Two additional patients, one who had V-R and the other V-D, are new suspects for recurrent ulcer.

Postoperative Gastric Studies

The insulin stimulation test described by Hollander was used to test for completeness of vagotomy. Valid tests were performed 937 times on 183 patients from six months to eight years after operation without complications. This data is summarized in Table 4 and does not include any test in which the blood glucose level failed

TABLE 4. *Results of Hollander Insulin Tests Performed Six Months to Eight Years after Operation*

	V-D			V-R		
	No. of Patients	No. Valid Tests	% Reduction in Maximal Histalog	No. of Patients	No. Valid Tests	% Reduction in Maximal Histalog
All patients	95	504		88	433	
All tests negative	40	193	82.6	76	378	97.1
Both pos. and neg. tests	37	236	71.8	9	50	89.8
All tests positive	18	75	64.1	3	5	74.5

TABLE 5. *Comparison of the Pre and Postoperative Basal and Maximal Histalog Gastric Secretory Responses*

		V-D Mean ± SD	V-R Mean ± SD
Basal	Preop.	9.2 ± 7.5	10.54 ± 11.6
(mEq HCl/2 hrs.)	6 Mo. Postop.	1.2 ± 2.3	0.05 ± 0.1
	5 Yrs. Postop.	1.4 ± 1.8	0.02 ± 0.1
Histalog	Preop.	64.8 ± 22.1	68.5 ± 23.8
(mEq HCl/2 hrs.)	6 Mo. Postop.	15.7 ± 12.6	3.3 ± 5.1
	5 Yrs. Postop.	13.5 ± 10.4	2.3 ± 4.9

SD = Standard Deviation.

to fall at least 50% below the control level and below 40 mg/100 ml. If a patient had one positive insulin test he was classified as having a positive Hollander test even if all other tests were negative. All insulin tests were negative in 42% of patients who had V-D and in 86% of patients who had V-R. Using these same criteria 50% of patients who had V-D and 87% who had V-R had negative tests at the time of the first report. Basal gastric secretion and the response to augmented histalog simulation were significantly reduced by both V-D and V-R (Table 5) but the reduction in both measurements was significantly greater after V-R than V-D. The reduction in the postoperative histalog tests compared with the preoperative tests was greatest in those patients in whom all the insulin tests were negative and least when all insulin tests were positive (Table 4). The data suggest that one can anticipate the completeness of vagotomy by noting the magnitude that acid secretion in response to histalog stimulation is decreased postoperatively in comparison to the preoperative response.

Evaluation of Results

The evaluations of the operative results made by the patients suggest that there were no differences between V-D and V-R with respect to the clinical results obtained (Table 6). The author's evaluations, though subject to possible bias, appeared more discriminating and more critical than those by the patients. Based on the results of a standard interview, patients were classified as: 1) "asymptomatic"; 2) "improved but not asymptomatic," although symptoms were not troublesome and were easily controlled; or 3) "symptomatic" that is, patient had symptoms of recurrence, early or late dumping, altered dietary habit, or diarrhea which required greater effort to control. The number of patients completely asymptomatic was greater after V-D than after V-R but when those patients who were asymptomatic and improved were combined there was no difference between V-D and V-R (Table 7). These results were nearly identical to those observed in the original report. Table 7 suggests that significant symptoms occurred in 5% of patients who had V-D and in 9% of patients who had V-R. However, if those patients who were reoperated for recurrent ulcer had been included in the group with significant symptoms instead of in the group who were asymptomatic, 13% of the patients who had V-D and 10% of those who had V-R would have fallen into that category with significant symptoms.

The clinical evaluations made by independent observers of patients who were three years postoperative are tabulated in Table 8. The percentage of patients totally asymptomatic after V-R was less than that suggested by the patient's evaluation and the same as that obtained by the author while the number of patients asymptomatic after V-D was much smaller than that recorded by either the patients or the author. The results of the evaluations made by independent observers and by the patients suggest that there was little difference in the clinical results obtained in these two groups of patients although the number of good results recorded by the independent investigators was less in both groups than was professed to exist by the patients.

TABLE 6. *Patient's Evaluation of Clinical Results*

Operation	Years Postop.	No. of Pts. Studied	Much Better	Some Better	No Change	Worse
V-D	5 to 8	86	78	7	0	1
	4 to 4.5	3	2	0	1	0
	Less than 4	14	12	1	0	1
		103	92 (89%)	8 (8%)	1 (1%)	2 (2%)
V-R	5 to 8	80	71	6	1	2
	4 to 4.5	7	5	2	0	0
	Less than 4	4	2	2	0	0
		91	78 (86%)	10 (11%)	1 (1%)	2 (2%)

TABLE 7. *Author's Evaluation of Clinical Results*

Operation	Years Postop.	No. of Pts. Studied	Asymptomatic	Number of Patients Improved, Not Asymptomatic	Significant Symptoms
V-D	5 to 8	86	67	15	4
	4 to 4.5	3	3	0	0
	Less than 4	14	12	0	2
		103	82 (80%)	15 (15%)	6 (5%)
V-R	5 to 8	80	48	25	7
	4 to 4.5	7	4	2	1
	Less than 4	4	2	2	0
		91	54 (59%)	29 (32%)	8 (9%)

Discussion

This study was initiated to determine objectively if either V-D or V-BI was a superior operation for treatment of duodenal ulcer. In the initial report it was stated that V-R could be done with a mortality equally as low as that associated with V-D if resection was avoided in those patients in whom it was technically difficult to work with the duodenum because of extensive inflammation in the area. It was concluded that V-R could be performed in the majority of patients as safely as V-D and, by so doing, those patients would not be subjected to the risk of recurrent ulcer which occurs with significantly greater frequency after V-D than after V-R. The original report failed to detect any clear-cut superiority between the two operations with respect to the frequency of other associated postoperative gastrointestinal symptoms. The data in this report are thought to be highly reliable because of the large percentage of patients followed at frequent intervals in person. They confirm the findings in the original report and no data is provided to significantly alter our original conclusions. Therefore when resection is considered technically safe V-R rather than V-D is preferred.

In the author's opinion, gastrointestinal symptoms appeared with greater frequency in the patients who had V-R than in those who had V-D. In the opinions of the patients and the independent investigators, however, the number of asymptomatic patients was similar after both types of operation although the independent investigator rated fewer patients asymptomatic than did the patients themselves. The symptoms which prevented the author from classifying a patient as totally asymptomatic were usually mild and easily controlled. It is therefore difficult to clearly state that V-D holds an advantage over V-R on the basis of the frequency or severity of postoperative gastrointestinal complaints although this may be the case.

Since the previous report, one additional patient with V-D and one with V-R have been reoperated for recurrent ulcer. Thus there have been nine (8%) recurrent ulcers and one suspected recurrent ulcer after V-D and one (1%) recurrent and one suspected ulcer after V-R. Failure of a significant number of recurrent ulcers to develop after the first report is consistent with the view that the majority of recurrent ulcers occur within the first two years after operation. It might be concluded that the cause for the higher recurrence rate after V-D was due to the greater potential for continued secretion of gastric juice after V-D than after V-R. This is reflected by the higher (58%) incidence of positive insulin tests after V-D than after V-R (14%), and the greater histalog response in those patients with positive insulin tests than in those with negative insulin tests. As stated in the earlier report, one of the advantages of antrectomy over a drainage procedure is its ability to compensate for an incomplete vagotomy. This was exemplified by the last patient to develop a recurrent ulcer after V-D. This patient had a positive insulin test on several occasions before reoperation. He has remained well and has had a negative insulin test for three years following antrectomy without further attempt at revagotomy.

The greater secretory potential after V-D than after V-R, however, does not appear adequate to account completely for the increased number of recurrent ulcers observed after V-D. The same number of positive insulin tests were reported after parietal cell vagotomy without drainage as after truncal vagotomy with drainage[4] yet a recurrent ulcer rate of less than 1% was reported by

TABLE 8. *Independent Physician's Evaluation of Clinical Results at Three Years*

Operation	No. of Pts.	% Asymptomatic	% Improved, Not Asymptomatic	% With Significant Symptoms
V-D	73	60	34	6
V-R	72	57	35	8

Johnston[2] after parietal cell vagotomy without drainage in patients in whom the number of positive insulin tests[3] was the same as we reported in patients with truncal vagotomy and drainage who had a recurrent ulcer rate of 8.3%. Since the pylorus is preserved after parietal cell vagotomy and destroyed or by-passed after truncal vagotomy, it is possible that the greater number of recurrent ulcers after truncal vagotomy is in part due to the elimination of the pyloric mechanism which is known to reduce reflux of duodenal contents into the stomach.

The consistency between the first report and this one with respect to the number of patients who had a positive insulin test does not support the concept that gastric secretion returns in time as a result of gastric reinnervation by nerve sprouting. It is more likely that a patient who has a negative insulin test one time and a positive test another time represents a patient in whom the factor responsible for a positive test was present initially. This factor may or may not be an incomplete vagotomy. In addition to the consistency in the number of patients in each category (V-D and V-R) with a positive insulin test, the mean basal acid output and the mean acid secretory response to histalog for each group were nearly the same at five years as they were at six months after operation. The fact that most recurrent ulcers occurred within two years of operation was related to the failure of these secretory tests to change significantly after that period of time. The greater response in these parameters after V-D than after V-R probably contributed to the increased number of recurrent ulcers after V-D but as stated above may not be the only factor responsible for this difference.

Our study, like that of Goligher,[1] fails to demonstrate a clear superiority of one operation over the other with respect to the occurrence of postoperative complications and gastrointestinal symptoms. Neither does the ability of patients to maintain an ideal weight postoperatively recommend one procedure over the other. Nevertheless, because of the better protection that V-R provides against recurrent ulcer, we prefer that operation rather than V-D when it appears that the duodenum can be dissected safely. There is, however, the possibility that metabolic deficits might become evident in patients followed for longer periods after V-R and negate the advantage resulting from a smaller number of recurrent ulcers. This has not yet become apparent.

The absence of operative deaths in the V-R group was partly fortuitous but more importantly it was due to the avoidance of resection in those patients with extensive inflammation in the vicinity of the duodenum. On the other hand, V-D was not an innocuous procedure. Among the patients who had V-D, there were two operative deaths, five times the number of patients with dysfunction of the stoma and four times the number of patients who required reoperation than there were in the V-R group. Thus it requires considerable skill to perform a pyloroplasty that does not leak and at the same time does not cause an unacceptable degree of obstruction. We realize that the use of V-R in all patients would be associated with a mortality significantly greater than that associated with the routine use of V-D. It is evident, however, from this study as well as others[6] that approximately 90% of patients (75% in Goligher's[1] study) can be treated by V-R equally as safe as V-D and that approximately 8% of these patients will be spared the risk of recurrent ulcer.

Other operations for treatment of duodenal ulcer will develop in time. Currently, highly selective vagotomy or parietal cell vagotomy without drainage[4] is receiving considerable attention. This operation has a great deal of appeal because of its relative simplicity and the paucity of associated undesirable gastrointestinal symptoms but before it is widely accepted and recommended it must be subjected to time consuming, rigorous, prospective, randomized studies similar to those that have been used to evaluate operations currently in general use.

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Congenital Partial Gastric Antral Obstruction,

An Elusive Cause of Abdominal Pain and Vomiting

MORTON M. WOOLLEY, M.D., * JOHN L. GWINN, M.D.,†
ABRAHAM MARES, M.D.‡

The patient with partial gastric antral obstruction due to a diaphragm may present with obstructive symptoms at any age in life. Including the four patients presented, there are now 50 reported cases. Since the diagnosis has been unduly delayed in many adults, it is particularly important that those physicians and surgeons caring for infants and children be aware of this entity. If properly treated in infancy and childhood, many years of suffering and debility can be obviated.

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IN 1942, Berman and Ballenger recorded the case history of a two-year-old boy who presented with a three week history of vomiting.[4] An upper gastrointestinal x-ray study revealed a partial obstruction of the pylorus. Surgical intervention revealed a pre-pyloric diaphragm with a small central aperture. The obstructing membrane was incised longitudinally through an anterior gastrotomy. The incision was closed transversely, thus alleviating the obstruction. The patient survived and became asymptomatic.

Since this first case report, there have been an additional 45 case reports of patients with gastric antral obstruction due to a mucosal diaphragm with a central or eccentric aperture causing *partial* obstruction.[2–33] We are adding four case reports to the collected series, making a total of 50 case reports available for review (Table 1). Case 22[18] was previously reported from this institution by Liechti *et al.*

Case Reports

Case 1. R.N. (CHLA #272242): This 2 year, 8 month-old Oriental boy was admitted to the hospital on September 27, 1964 because of vomiting of two weeks duration resulting in weight loss of 6 lb (2.72 kg). Prior to this episode, he had had no gastrointestinal symptoms. His mother and father, as well as two siblings, along with the patient, suffered from what appeared to be epidemic gastroenteritis characterized by nausea, vomiting and diarrhea. The other members of the family recovered, but the patient continued to vomit and eventually developed hypochloremic alkalosis (serum chlorides 71 mEq/l and CO_2 combining power 37 mEq/l). His weight was 26 lb (11.8 kg), less than 16th percentile, and he had a visible epigastric peristaltic wave progressing from the left upper quadrant across the epigastrium. An upper gastrointestinal barium study revealed obstruction of the gastric antrum due to a diaphragm which allowed only a small amount of dye to pass through it (Fig. 1). After appropriate fluid and electrolyte replacement, the patient was operated upon on October 1, 1964. The external surface of the stomach was quite normal. A Foley catheter was introduced into the duodenum through a small anterior gastrotomy (Fig. 2). After the bag had been inflated it was pulled back through the pylorus and was noted to impinge on the antral diaphragm (Fig. 3). The diaphragm was resected by performing a sleeve resection of the distal stomach (Fig. 4). A gastrostomy was left in place for postoperative decompression

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TABLE 1. *Resume of Fifty Clinical Cases of Gastric Antral Diaphragm Including Forty-Six from the Literature and Four Currently Presented Cases*

Author	Year	Sex	Age	Presenting Symptom	Duration	Associated Findings	Operation	Results
1. Berman & Ballenger[4]	1942	M	2 years	vomiting	3 weeks		gastroplasty	cured
2. Sames[27]	1949	F	40 years	epigastric pain vomiting	6 years 2 years	gastric ulcer	gastrectomy gastrojejunostomy	not stated
3. Gross & Durham[12]	1953	F	35 years	intermittent vomiting	"several years"	appendectomy & 4 pelvic operations for symptoms without relief	gastro-pyloro-plasty	cured
4. Rota[26]	1953	F	74 years	nausea, vomiting, diarrhea	8 years	labeled "neurotic"	partial gastrectomy	cured
5. Albot & Magnier[1]	1955	M	32 years	epigastric pain, vomiting	3 years		gastric resection	cured
6. Passalacqua & Romero[22]	1955	M	62 years	epigastric pain, fullness, nausea and vomiting	12 years	patient operated upon in 1949, surgeon did not recognize lesion at that time	partial gastrectomy	not stated
7. Swartz & Shepard[32]	1956	F	55 years	nausea and vomiting, weight loss of 65 lb	not stated		gastro-pyloro-plasty	cured
8. Bariety, Poulet, & Courtois-Suffit[3]	1957	M	52 years	anorexia and vomiting	4 months		gastroplasty	cured
9. Despirito & Guthorn[9]	1957	M	3 weeks	vomiting	3 weeks	meconium peritonitis		recovered
10. Chamberlain & Addison[6]	1959	F	55 years	early satiety, weight loss of 15.9 kg	8 months		partial gastrectomy and gastrojejunostomy	cured
11. Chamberlain & Addison[6]	1959	M	52 years	epigastric pain and vomiting	6 months		gastrectomy and gastrojejunostomy	cured
12. Rhind[25]	1959	M	68 years	painful dyspepsia vomiting	23 years 15 years	2 gastric ulcers	gastric resection	not stated
13. Rhind[25]	1959	M	54 years	abdominal pain and vomiting	1½ years		gastric resection	not stated
14. Young[33]	1961	F	53 years	early staiety	"several years"	"Addisonian pigmentation"	partial gastrectomy and jejunostomy	cured
15. Kenny[16]	1962	F	53 years	epigastric pain, indigestion, vomiting	10 years	lesser curvature gastric ulcer	partial gastrectomy and gastro-jejunostomy	not stated
16. Kenny[16]	1962	F	49 years	"ulcer symptoms"	12 years	several gastric ulcers 1 cm. in diameter	not stated	not stated
17. Kenny[16]	1962	F	65 years	vomiting, weight weight loss of 28 lb	9 months	gastric ulcer	not stated	not stated
18. Kenny[16]	1962	F	66 years	vague ulcer history	"several years"	gastric ulcer	not stated	not stated
19. Popesco-Urluieni, Bacalou & Mayer[23]	1962	F	45 years	epigastric pain and vomiting	3 years		gastrectomy and gastrojejunostomy	patient expired due to postoperative leak of duodenal stump & perforated gastric ulcer
20. Stahl[31]	1963	F	62 years	epigastric distress and vomiting	15 years		excision of diaphragm and gastro-pyloro-plasty	cured
21. Liechti, Mikkelsen, & Snyder	1963	F	4 years	vomiting	2 years	anemia	biopsy of diaphragm and gastroplasty	cured
22. Munro[19]	1963	M	56 years	indigestion, belching and vomiting	"several years"		excision of part of diaphragm and transverse closure of gastrotomy	cured

TABLE 1. (*Continued*) *Resume of Fifty Clinical Cases of Gastric Antral Diaphragm Including Forty-Six from the Literature and Four Currently Presented Cases*

Author	Year	Sex	Age	Presenting Symptom	Duration	Associated Findings	Operation	Results
23. Sokol, Shorofsky & Werther[29]	1963	F	29 years	upper abdominal distress and weakness, sweating and pallor after meals	"long history"		gastroscopy for diagnostic purposes; patient refused surgery	not stated
24. Browning[5]	1964	M	62 years	epigastric distress, vomiting	10 years 3 years		excision of septum and transverse closure of gastrotomy	cured
25. Gerber[11]	1965	M	2½ years	vomiting	4 weeks		incision of diaphragm and gastro-pyloroplasty	cured
26. DeBoer[8]	1965	F	11 years	vomiting	"since infancy"	patient received psychotherapy for vomiting	not stated	not stated
27. Knepper[17]	1965	M	16 years	abdominal distress	15 years		gastrectomy and gastrojejunostomy	cured
28. Ittzes[14]	1965	M	69 years	early satiety	"all of life"		gastric resection and gastroduodenostomy	cured
29. Pulsifer, Jedd and Van Zandt[24]	1965	F	61 years	abdominal pain and vomiting	25 years		V-division of membrane and gastro-pyloroplasty	cured
30. Parrish, Sherman, & Moretz[21]	1966	F	54 years	postprandial fullness, nausea and vomiting	"many years"		vagotomy, antrectomy and gastrojejunostomy	cured
31. Schwartz, Hirsch, Mule & Bluestone[28]	1966	F	74 years	upper abdominal pain, vomiting and pyrosis	20 years	cholecystectomy three months previously did not relieve symptoms	excision of diaphragm and gastro-pyloroplasty	cured
32. Banks, Waye, Waitman & Cornell[2]	1967	F	62 years	epigastric pain, nausea and vomiting	12 years		antrectomy and gastroduodenostomy	cured
33. Spencer[30]	1967	M	53 years	ulcer synptoms vomiting BUN 204	13 years 4 months	mentally confused	excision of membrane and transverse closure of gastrotomy	cured
34. Parrish, Kanavage, Wells & Moretz[20]	1968	M	59 years	anorexia, weight loss epigastric pain, nausea vomiting	2 years		excision of membrane, vagotomy and pyloroplasty	cured
35. Parrish, Kanavage, Wells & Moretz[20]	1968	F	6 years	vomiting and abdominal pain	4 days	passage of Ascaris by mouth and rectum	excision of membrane and pyloroplasty	cured
36. Parrish, Kanavage, Wells & Moretz[20]	1968	F	56 years	nausea, vomiting and epigastric pain, weight loss of 55 lb	1 year		excision of diaphragm	cured
37. Parrish, Kanavage, Wells & Moretz[20]	1968	F	67 years	nausea and vomiting	6 months		50% gastrectomy and gastroduodenostomy	cured
38. Felson, Berkmen & Hoyumpa[20]	1969	M	78 years	vomiting, epigastric pain and weight loss	3 years		gastro-pyloroplasty	cured
39. Felson, Berkmen Hoyumpa[10]	1969	M	74 years	nausea and vomiting and weight loss of 30 lb	2 years		excision of diaphragm and pyloroplasty	cured
40. Felson, Berkmen & Hoyumpa[10]	1969	M	41 years	epigastric fullness belching and vomiting	18 years		excision of diaphragm, vagotomy and pyloroplasty	cured

TABLE 1. *(Continued) Resume of Fifty Clinical Cases of Gastric Antral Diaphragm Including Forty-Six from the Literature and Four Currently Presented Cases*

Author	Year	Sex	Age	Presenting Symptom	Duration	Associated Findings	Operation	Results
41. Felson, Berkmen & Hoyumpa[10]	1969	F	84 years	epigastric pain	40 years		none	patient died of cardiovascular disease and pulmonary embolism; autopsy revealed pyloric diaphragm with duodenal mucosa on one side and gastric mucosa on the other
42. Cremin[7]	1969	F	3 days	non-stained emesis			not described	not given
43. Cremin[7]	1969	M	4 days	emesis	4 days		not described	not given
44. Cremen[7]	1969	?	newborn	meconium peritonitis			resection of membrane	not given
45. Johnson[15]	1971	M	12 years	vomiting	11 years		gastro-pyloroplasty	cured
46. Hait, Esselstyn, & Rankin[13]	1972	F	67 years	"ulcer"	9 years		vagotomy (prior to recognition of lesion), followed by distal gastrectomy, resection of gastric ulcer and Billroth I duodenostomy	cured
47. Woolley, Mares & Gwinn	1972	M	28,10	vomiting	2 weeks		distal gastrectomy and gastroduodenostomy, gastrostomy	cured
48. Woolley, Mares & Gwinn	1972	M	8 months	vomiting, loose, foul smelling stools	"since birth"	Salmonella in the stool	gastro-pyloroplasty	cured
49. Woolley, Mares & Gwinn	1972	F	4 years	agdominal pain, vomiting ,melena melenemesis (treated for ulcer disease)	2 years		distal gastrectomy and gastroduodenostomy	cured
50. Woolley, Mares & Gwinn	1972	F	2 days	vomiting and abdominal distention	"since birth"	malrotation and colon atresia	ileostomy, resection of antral diaphragm and gastropyloroplasty, lysis of Ladd's bands, gastrostomy	patient expired from necrotizing enterocolitis and sepsis on the 12th postoperative day

(Fig. 5). Gastric emptying was delayed for eight days. Since then the patient has been eating and developing normally. The pathology report was that of a diaphragm covered with gastric mucosa on both sides.

Case 2. B.H. (CHLA #298239): This patient was first admitted to the hospital on March 13, 1966 at eight months of age because of "Malabsorption syndrome." Vomiting and diarrhea had been present since birth and many formula changes as well as treatment with pancreatic granules had been ineffective in relieving the symptoms. The patient's weight was 15 lb, 14 oz (7.3 kg) which was below the 16th percentile. Bacteriological examination of the stool revealed Salmonella. An upper gastrointestinal study was consistent with gastric antral diaphragm. The patient was treated for the Salmonella infection and discharged from the hospital. He was readmitted and operated upon on February 2, 1967 at 18 months of age. Digital examination of the antrum revealed an obstructing lesion consistent with an antral diaphragm. This was biopsied, transected longitudinally, and closed transversely thus alleviating the obstruction. Postoperatively, the patient recovered and was able to eat and gain weight appropriately. The pathology report was that of gastric mucosa only.

Case 3. S.R. (CHLA #357892): This four-year-old girl was admitted to the hospital on November 3, 1968 because of abdominal pain, melena and melenemesis of two years duration. During these two years, she had been on a medical regimen for peptic ulcer disease. Her weight was 30 lb (13.5 kg) which was below the 16th percentile. An upper gastrointestinal x-ray study revealed partial gastric antral obstruction due to a diaphragm (Fig. 6). On November 3, 1968 the patient underwent distal gastrectomy thus removing the diaphragm which had a central opening of 4 mm in diameter. Gastroduodenostomy and gastrostomy were accomplished as in case 1. The patient recovered and is asymptomatic. The pathology report was that of a diaphragm with gastric mucosa on both sides.

Case 4. E.O. (CHLA #374075): This two-day-old infant was admitted to the hospital on July 23, 1969 because of vomiting and lack of stooling. Through the anterior abdominal wall one could readily discern dilated loops of bowel (Fig. 7). Roentgenograms revealed a gasless abdomen except for a small area of gas in the stomach (Fig. 8). The infant was operated upon at three days of age on July 24, 1969. A gastric antral diaphragm with a small central ostium was found and resected. The surgical pathology report revealed muscular tissue only with no mucosal covering apparent. The longitudinal gastroduodenal incision was closed transversely. The distal ileum was exteriorized because of colon atresia and Ladd's bands were lysed because the infant also had malrotation. Gastrostomy was performed for postoperative decompression. The patient progressed well until July 28, 1969 (fourth postoperative day) at which time excessive ileostomy fluid loss occurred. She was rehydrated, but on the eleventh postoperative day the ileostomy became necrotic and there were numerous areas of cutaneous gangrene. The hemoglobin level dropped to 7.2 gm%, pseudomonas was cultured from the ileostomy as well as from the nasopharynx. The patient expired on the 12th postoperative day to generalized pseudomonas sepsis.

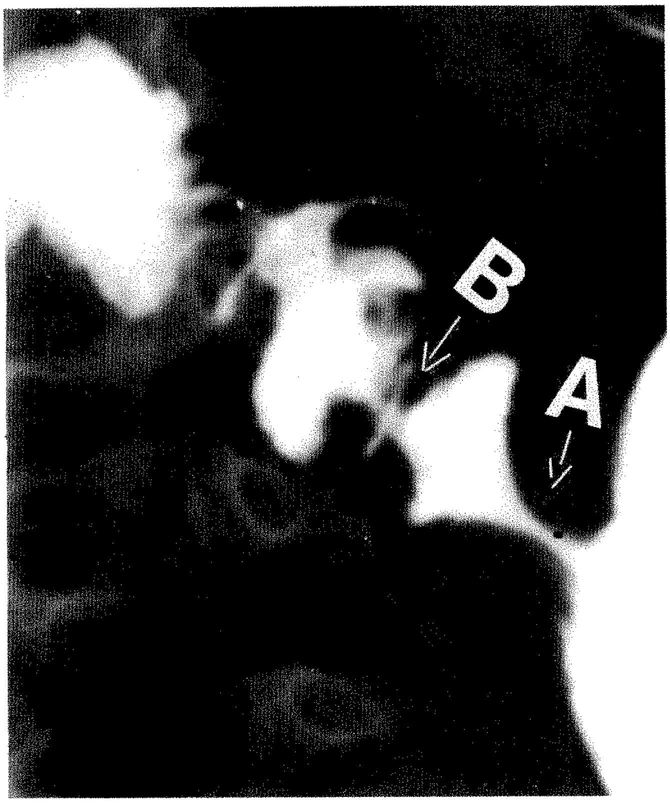

Fig. 1. Roentgenogram of gastric antral diaphragm. Arrow A points to vigorous peristaltic wave resulting from partial obstruction. Arrow B points to the diaphragm itself.

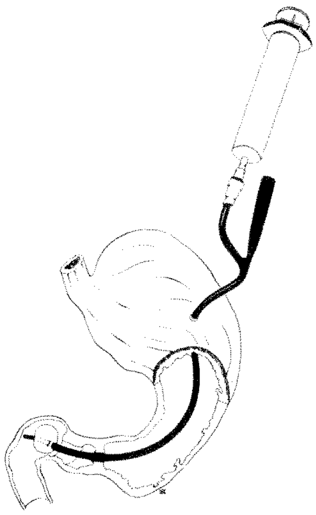

Fig. 2. Foley catheter passed through gastrostomy into the duodenum.

Discussion

Diagnosis

The patient who is born with complete obstruction of the alimentary tract has definite, persistent symptoms which should lead to early diagnosis and appropriate surgical therapy. In contrast, the patients reported in this series have a *partially* obstructing lesion which may result in either intermittent symptoms or delayed onset of obstructive symptoms leading to erroneous diagnosis, inappropriate medical treatment, eventual fluid and electrolyte losses, prolonged debility or multiple unhelpful operations. The majority of patients have the diagnosis established in the first, sixth or seventh decades of life (Fig. 9). The duration of symptoms in the adult population is frequently long enough that one can only speculate as to whether the duration was even longer than stated because the patient had never really experienced normal gastric emptying (Fig. 10). Most commonly, the patients were treated erroneously for peptic ulcer disease.

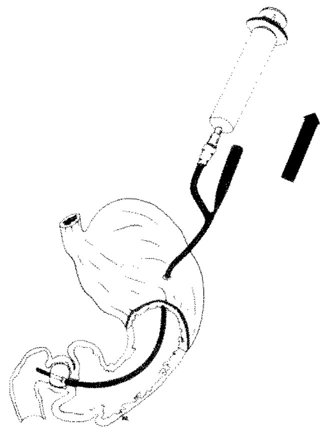

Fig. 3. After pulling the balloon through the pylorus it impinges on the diaphragm and pleats the stomach so that the location of the diaphragm can be accurately ascertained prior to opening the stomach or duodenum.

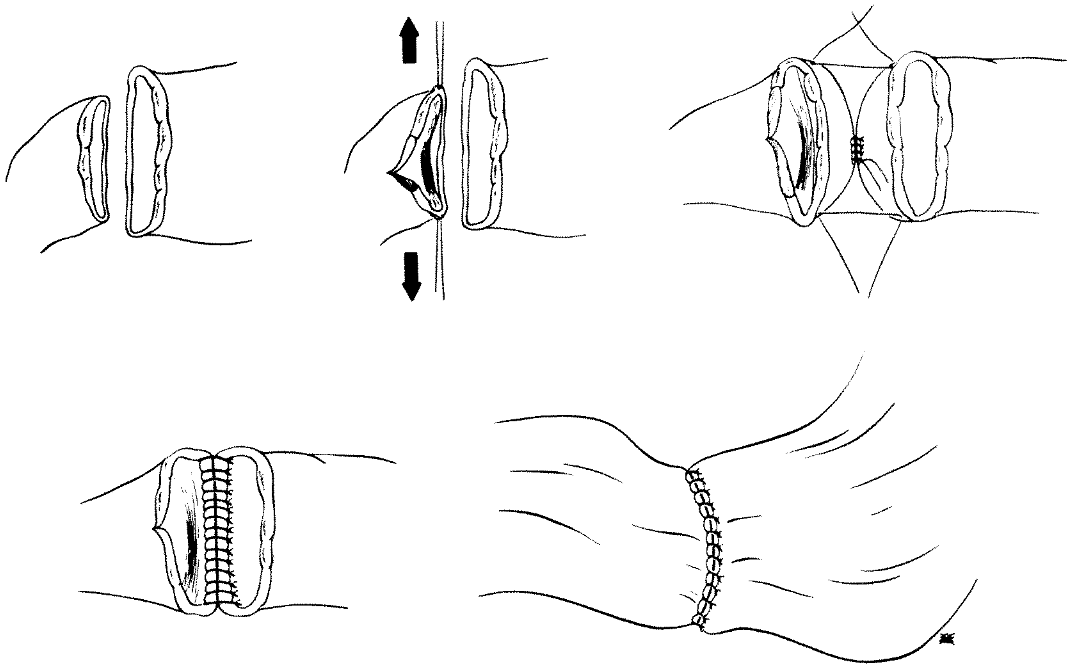

FIG. 4. After the diaphragm has been resected, the distal stoma is enlarged by incising the stomach and duodenum longitudinally across the pylorus. This allows an end-to-end anastomosis between the proximal and distal lumens. Since the pyloric ring is transected, this inherently adds pyloroplasty to the procedure.

An accurate diagnosis can usually be made by appropriate x-ray examination. Plain films of the abdomen may suggest obstruction due to dilated stomach; however, this is not diagnostic and contrast studies should be performed. We prefer to use barium introduced via a nasogastric tube. Water soluble media should not be used because with the partially obstructing lesion the detail may be inadequate for diagnosis.

Forceful peristalsis is frequently seen to the level of the antral diaphragm. There may be a delay in passage of the contrast and a persistent radiolucent line crossing the pre-pyloric region (Fig. 6). It is important that this radiolucent line be seen in profile. In contrast to hypertrophic pyloric stenosis, the lumen of the distal antrum is not narrowed or elongated. Although antral ulcers in the neonate are uncommon, the radiographic appearance of an ulcer may mimic that of antral diaphragm, therefore a definite ulcer niche should be demonstrated to differentiate the two.

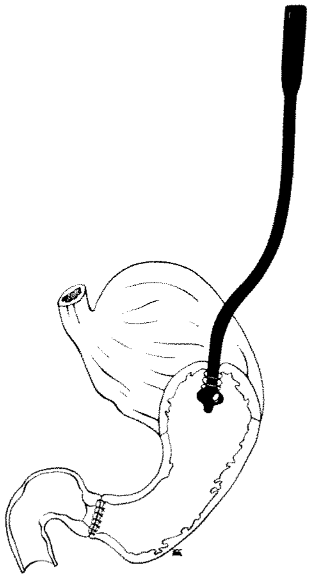

FIG. 5. A gastrostomy catheter is left in place thereby obviating the necessity of a nasogastric tube postoperatively. This is more comfortable for the patient and decreases nasopharyngeal, pulmonary, as well as esophageal irritation.

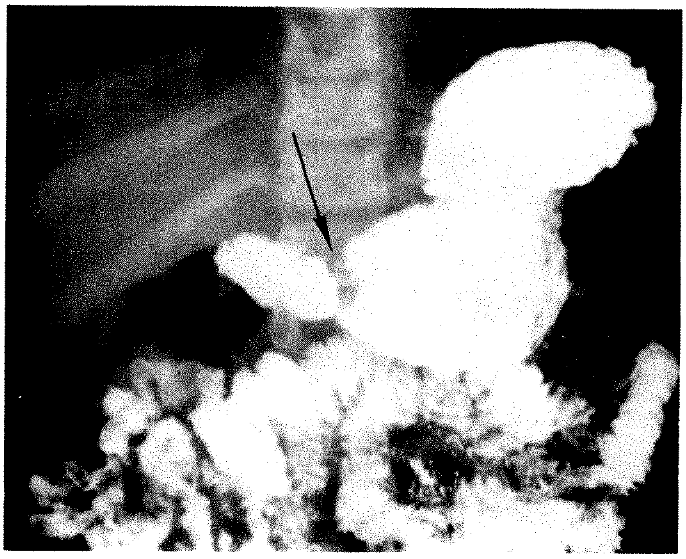

FIG. 6. X-ray appearance of antral diaphragm in case 3. The arrow points to the diaphragm. To the left of the diaphragm is the well-formed gastric antrum between the pylorus and the diaphragm.

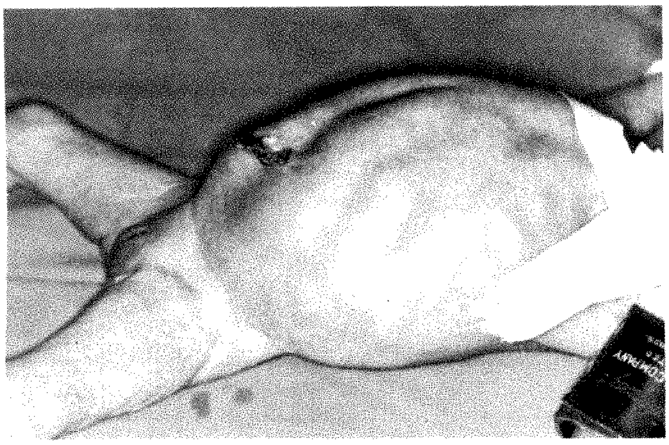

FIG. 7. Case 4—loops of bowel visible through the abdominal wall of infant with gastric antral diaphragm and colon atresia.

At the time of operation, the single most important maneuver which will define the *presence* and *location* of a diaphragm is to pass a Foley or Fogarty catheter into the duodenum and after the balloon is inflated, pulling it back so that it impinges on the diaphragm (Fig. 3). This will obviate time-consuming maneuvers in looking for the diaphragm since the external surface of the stomach may appear quite normal. Case 6 in Table 1[6] is a case in point where the lesion was overlooked at the time of the first operation.

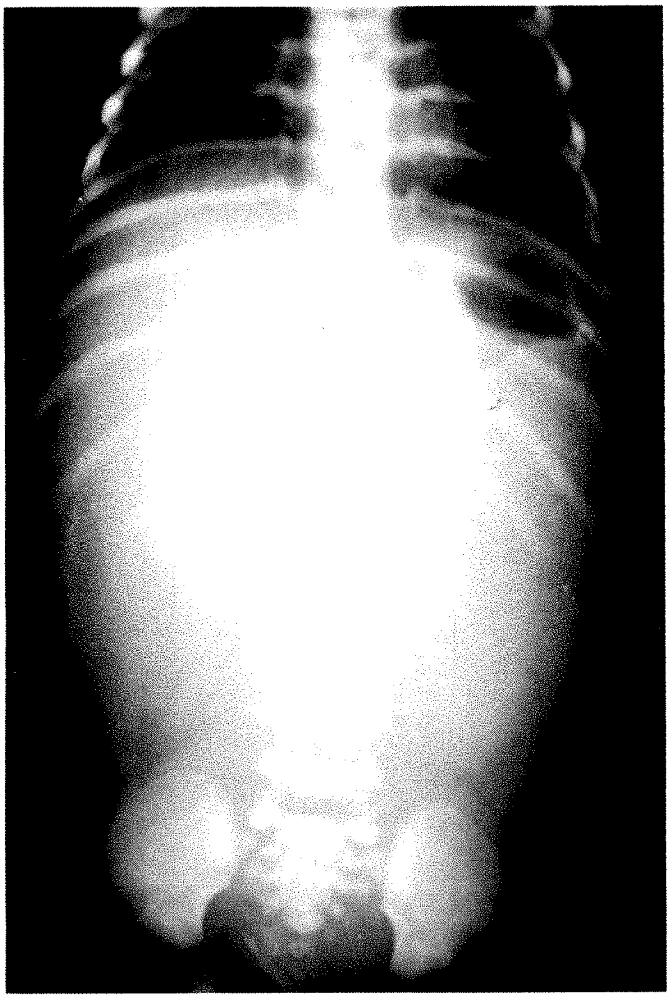

FIG. 8. Case 4—plain film of abdomen showing gasless abdomen distal to gastric bubble. The dilated loops of bowel were filled with fluid but no gas had progressed beyond the stomach.

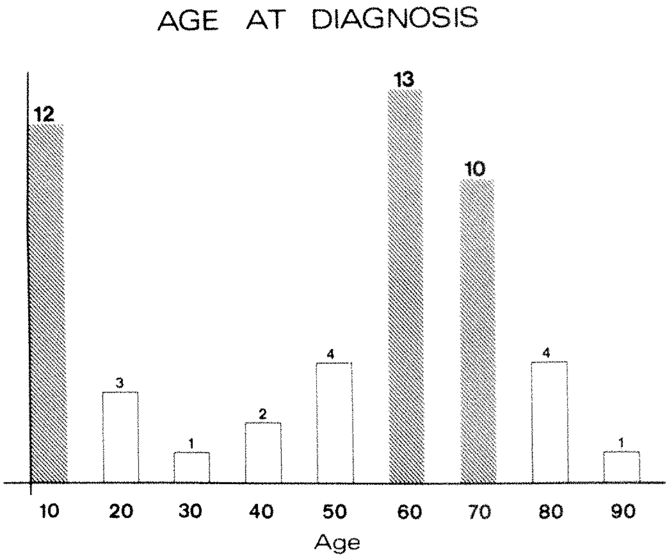

FIG. 9. The diagnosis of gastric antral diaphragm is most commonly made in the first, sixth, and seventh decades of life.

Pathology

If the entire diaphragm and adjacent gastric wall are removed, one can visualize the small ostium lined with

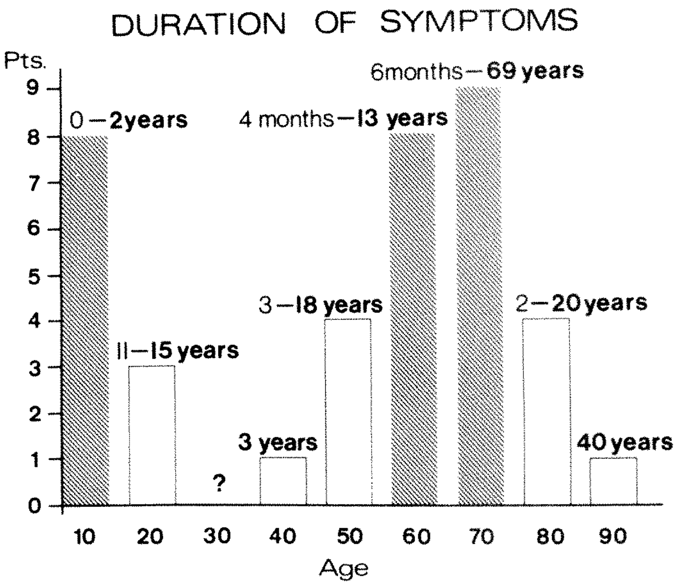

FIG. 10. The extremes of duration of symptoms prior to diagnosis are indicated in this graph. Note that one patient at age 69 years had been symptomatic for her entire life. Many patients have had debilitating illness for many years prior to definitive diagnosis and therapy.

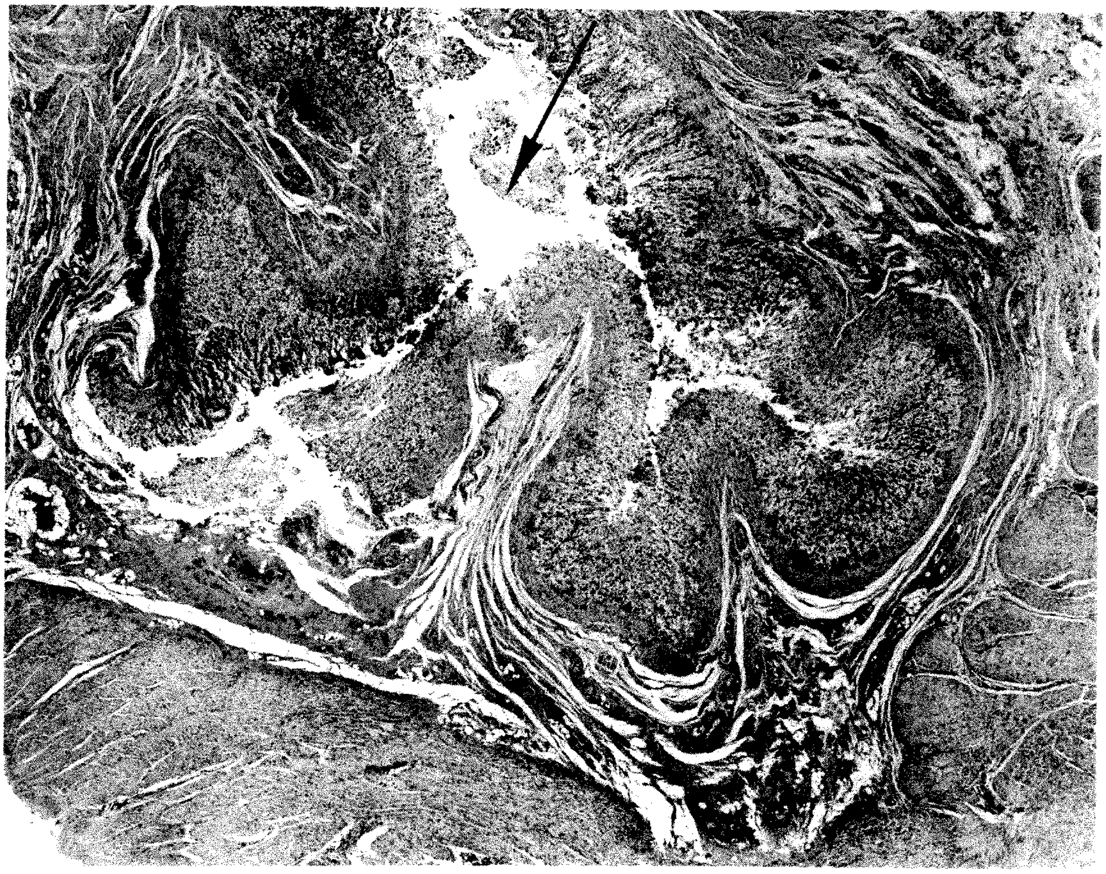

FIG. 11. Photomicrograph of the central portion of a gastric antral diaphragm. Notice the very small opening (arrow) surrounded by gastric mucosa.

gastric mucosa (Fig. 11). If only part of the diaphragm is removed, or if the area has been ulcerated, then one may only see muscular layers.

Therapy

The treatment of choice is clearly surgical once the diagnosis has been established. As long as the obstruction is alleviated, it appears that there is no preference for one particular operation over another. The choices are as follows:

1. Distal gastrectomy with gastroduodenostomy.
2. Longitudinal opening with transverse closure.
3. Resection of the diaphragm.
4. A combination of numbers two and three.

Although symptoms of the dumping syndrome might be expected if the pylorus is destroyed, this has not been our personal experience nor has it been reported in the literature. The diaphragm is quite close to the pylorus so that in some instances it would be difficult to remove the diaphragm without destroying the pyloric ring.

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Study of the Role of the Splanchnic Organs in Hepatic Atrophy for the Purpose of Auxiliary Transplantation of the Liver

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Many problems must be solved before auxiliary liver transplantations can be performed successfully in animals and in humans. The most important is the atrophy of the graft. To investigate the cause of this atrophy we have done experiments with seven series of dogs. We performed organ removals (splenectomy, pancreatectomy) and shunts (splenocaval derivation, mesenterico-caval shunt, spleno-mesenterico-caval shunt). Five to eight dogs were used in each series. Hepatic biochemical tests, determination of hepatic blood flow (by 198 Au, ^{90}Kr, Bengal Rose, Indocyanine Green) and serial liver biopsies before and after surgery (and in the long survivals) were included in the study. Results have shown a flow decrease of 32.3% ± SD 12.0 and 20.6% ± SD 5.2 after mesenterico and spleno-cava derivations. Histologically, a swollen cytoplasm was encountered (probably due to this important flow decrease); but we did not find any modifications of the cells (atrophy) nor of their fat and glycogen contents. On the other hand, after pancreatectomy (flow decrease of 14.2% ± SD 7.6) we found liver cord atrophy, bile retention, important fatty degeneration and disappearance of glycogen. All of these modifications were avoided by giving insulin subcutaneously after pancreatectomy. These results suggest that graft atrophy after auxiliary liver transplantation is due in part to an insufficient supply of insulin.

THE CAUSE of hepatic atrophy is still a matter of discussion, but it is of primary importance in the auxiliary transplantation of the liver[2,7,11] and in the physiopathology of cirrhoses of that organ.[9] It has been shown that when the liver is deprived of splanchnic blood it atrophies even if an equivalent output is provided by a supply of either arterial or venous systemic blood.[10,11]

An indispensable step towards perfection in auxiliary transplantation of the liver, already undertaken in the past in our laboratories,[16,17] would be the identification of the existence or nature of substances in the blood that might be responsible for this phenomenon of atrophy. Experimental operations based on a variety of shunted blood vessels, and excision of isolated or associated organs in dogs was therefore undertaken, together with measurements of blood flow and studies of liver structure and function.

Material and Methods

Sixty-eight mongrel dogs were operated under general anesthesia with Nembutal. They were divided into the following groups: the first group (shunts) consisted of three series: spleno-caval shunt (SCS); mesenterico-caval shunt (MCS); spleno-mesenterico-caval shunt (SMCS). The second group (excision of organs) consisted of two series: Pancreatectomy (PyX.); Splenectomy (SyX.). The third group (combinations) consisted of three series: spleno-caval shunt and splenectomy (SCS + SyX.); Mesenterico-caval shunt and pancreatectomy (MCS + PyX.); Pancreatectomy + sub-cutaneous insulin (PyX. + Ins.). Each series included a minimum of seven dogs. In each case the following tests were studied once a week: total proteins, bilirubin, transaminases, alkaline phosphatase, and prothrombine. In addition, biopsies were performed before and after surgery and every 10 days to study hepatic cellular integrity and to investigate cellular atrophy, fats, and the glycogenic load of the cell. These biopsies were performed during surgery by peripheral excision of a fragment 1 cm × 1 cm with a scalpel. After excision of the capsule,

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TABLE 1. *Decrease in Per Cent of Total Hepatic Blood Flow and Portal Blood Flow*

Shunts	Number of Dogs	Total Hepatic Blood Flow (Per cent Decrease)	Portal Blood Flow (Per cent Decrease)
MCS*	7	32.3 ± SD 12.0	47
SCS†	7	20.6 ± SD 5.2	31
PyX.‡	9	14.2 ± SD 7.6	21
SyX.§	7	1	
MCS + PyX.	7	45.2 ± SD 9.8	68
SMCS ‖	7	53.5 ± SD 11.2	78
SCS + SyX.	7	21.2 ± SD 5.4	31

* Mesenterico-caval shunt.
† Spleno-caval shunt.
‡ Pancreatectomy.
§ Splenectomy.
‖ Spleno-mesenterico-caval shunt.
Results are given as per cent decrease ± standard deviation

one portion was placed in Bouin's fluid, the other in formol. The material was kept at 4 C, and two specimens were taken of each. Histological study was performed by two different observers who were unaware of both the type of surgery performed and time of removal of the biopsy fragments. Two dogs with MCS and two dogs with SCS were sacrificed after one year and were studied histologically.

The total hepatic blood flow was computed by colloidal gold uptake (^{198}Au). The total flow calculated by this method was expressed as a percentage of the normal. The hepatic blood flow was measured using a method based on colloidal gold clearance, giving values of change rather than absolute flow rates. This relative method was preferred to other techniques using flow meters or radioactive gases.[5,6] The technique used here is simple, well adapted to the operating room, yields results that are reproducible when the measurements are made over a short time span.[5,6] The portal venous blood flow was then calculated as based on data available in the literature.[1] This was verified by data from a control group of dogs.[5]

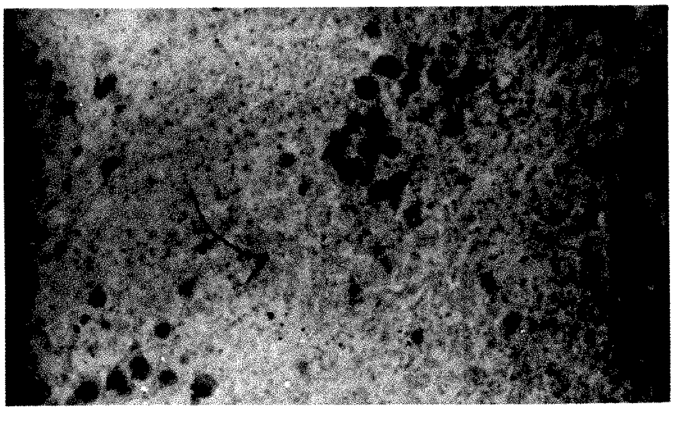

FIG. 1. Mild fatty degeneration as shown by sudan stain after spleno-caval shunt (SCS).

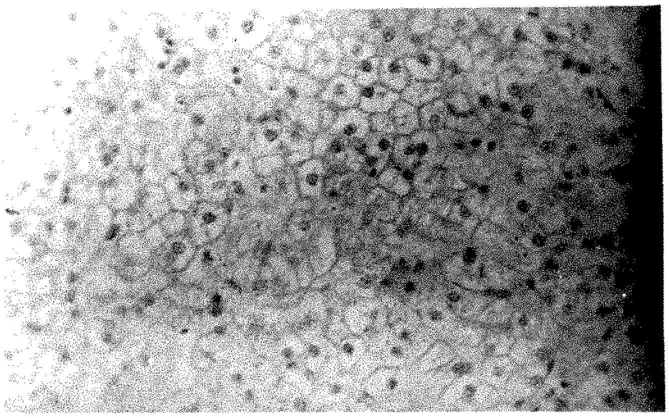

FIG. 2. Cellular edema after mesenterico-caval shunt (MCS). The same aspect has been found after spleno-mesenterico-caval shunt (SMCS).

Results

The results obtained in the various shunts showed that no shunts caused definite modifications in the various hepatic biochemical parameters which we studied.

The SCS (Table 1) causes an average drop in the total hepatic blood flow of 20.6% ± SD 5.2 (with extremes of 32%). Histologically (Fig. 1), no atrophy was discovered; the microscopic aspect was normal in four cases. In three cases corresponding to the greatest drops in flow in excess of 30%, moderate fatty degeneration was observed, combined with an edematous appearance of the hepatic cell.

MCS and SMCS (Table 1) cause modifications in the total hepatic blood flow of 32.3% ± SD 12.0 and 53.5% ± SD 11.2 respectively or 47% and 78% of the portal flow. Histologically, no atrophy was found. A clear-cut fatty change and an aspect of cellular edema were the only factors noted in all cases (Fig. 2). This aspect was especially evident in two dogs sacrificed after one year.

The SyX. (Table 1) always caused drops of less than

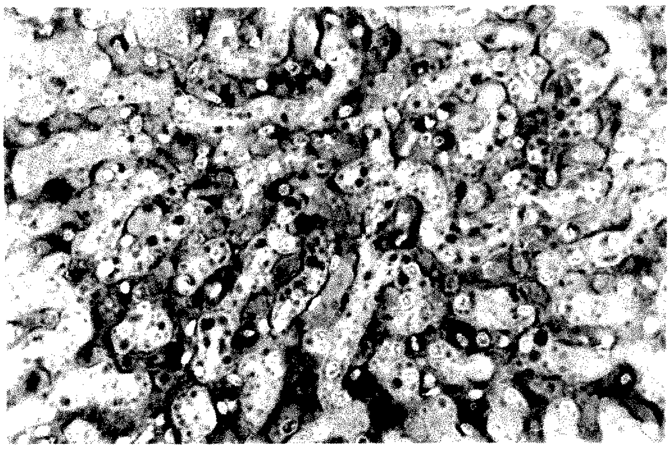

FIG. 3. Liver cord atrophy after pancreatectomy (PyX.).

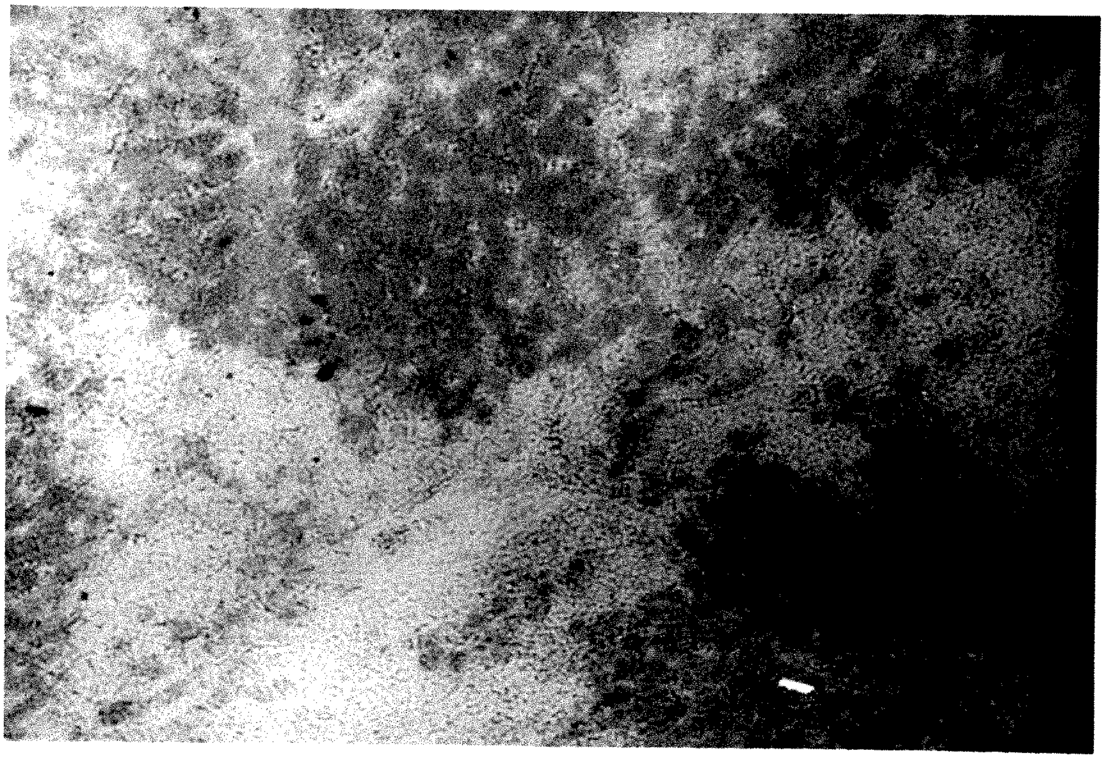

FIG. 4. Severe fatty degeneration after pancreatectomy (PyX.).

1% in output. In all cases there were no histological modifications. The PyX. caused a decrease of 14.2% ± SD 7.6 in total hepatic output, or 21% of the portal output. Histological study showed atrophy of the hepatic cords (Fig. 3) combined with signs of bile retention (biliary thrombi in the canalicules), a severe fatty change (Fig. 4), and a massive deglycogenation (Fig. 5). It should be noted that these signs appeared early, being clearly visible on the third day following the PyX. All of these modifications were absent when pancreatectomy was performed in combination with subcutaneous administration of insulin (Fig. 6). MCS combined with PyX. enabled us to reproduce the histological modifications observed after isolated PyX. In these cases the drop in total hepatic output was 45.2% ± SD 9.8 (Table 1).

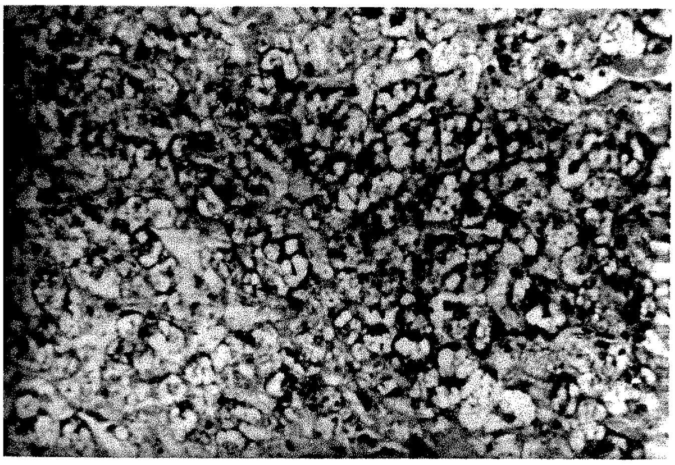

FIG. 5. Massive deglycogenation after pancreatectomy (PyX.).

Discussion

Despite the great number of works on the subject,[2,3,8,12,17,19–22] the problem of hepatic atrophy in auxiliary transplantation of the liver has never been satisfactorily solved. Certain authors have shown that apart from immunological phenomena, the liver, when deprived of splanchnic blood, atropied because of the lack of a supply of trophic substance(s),[11,12,] or because the systemic supply replacing the substance(s) does not adequately meet the outflow and the pressure conditions that seem to be necessary for its proper functioning,[22,23] or because of competition between the transplanted liver and the liver of the recipient.[15,22]

Our contributions to the study of this problem are of two kinds. On the one hand they reveal that beyond a drop of 30% in the total hepatic blood flow, very definite signs of cellular stress appear that are characterized essentially by a cellular edema.

It is obvious that this element should be given careful consideration, since rejection itself causes a drop in flow in the small blood vessels. The transplanted liver should be placed in the best possible vascular conditions. However, the drop does not explain the atrophy, nor the fatty change, nor the deglycogenation. We must look, then, for a substance originating in one of the splanchnic organs. Our experience with the pancreas transplantation preceded by the PyX. of the recipient[18]

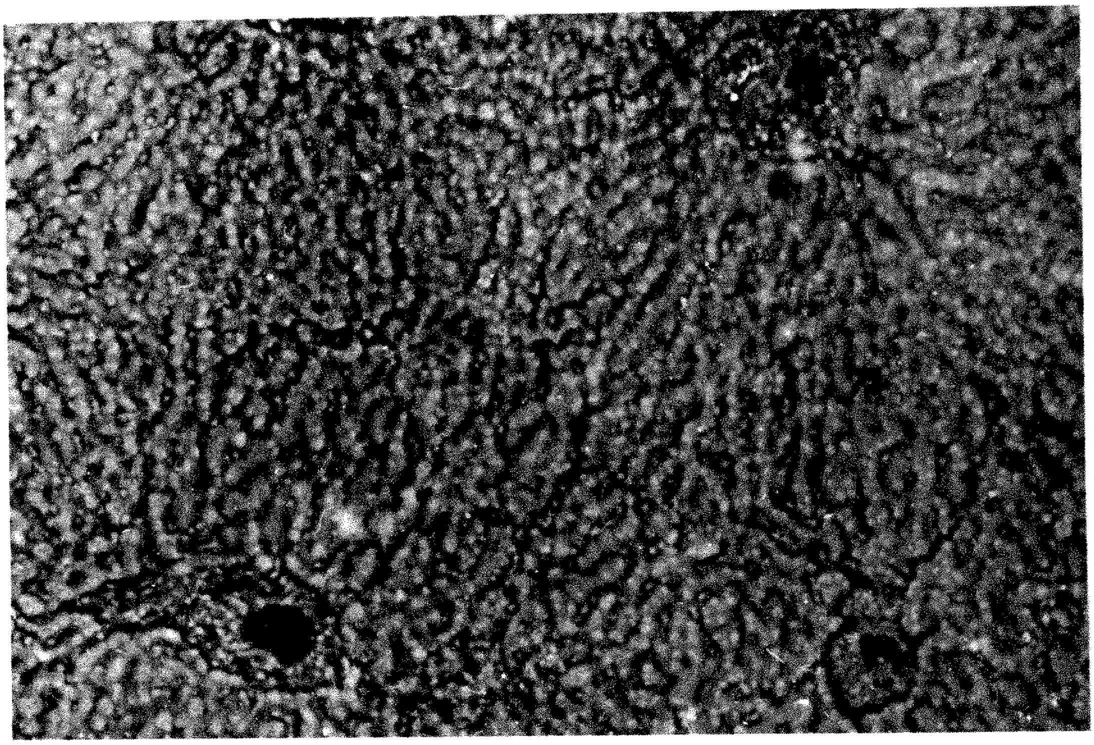

FIG. 6. Normal liver (hematin-eosine stain) after pancreatectomy in a dog given insulin subcutaneously.

had already revealed the major role which could be played by the pancreas in the appearance of hepatic atrophy, and had led us, in a first phase, to perform a series of auxiliary transplantations of the hepato-enteric block so that in a second phase we could select the most adequate intestinal segment to be transplanted with the liver.[16,17] Moreover, the trophic role of the pancreas has recently been stressed.[13] Upon examination of the results presented, the intestine, duodenum, stomach and spleen seem to have no trophic effect on the liver. Only the cases creating a drop in the total hepatic output greater than 30% (MCS and SMCS and several cases of SCS) caused a cellular stress marked by an edema of the hepatic cell. In contrast, PyX. produces a major hepatic atrophy which appears very early, and which is not explained by the minimal drop in output. These disturbances seem to be corrected by a systemic supply of insulin, which could thus be a prime trophic hormone for the liver.

However, the absence of serious trophic disturbances after MCS and SMCS, which can be attributed to the presence of the pancreas, could possibly be linked to a recycling, from the systemic circulation to the portal circulation, of a trophic substance originating in the intestine and amply discharged into the systemic circulation because of the shunt. The studies made by Price *et al.*,[14] achieving complete evisceration of the splanchnic organs with systemic supply of insulin, are not guided along the same lines, but they confirm our findings.

What, then, is the explanation for the fact that certain authors[20,21] observed no atrophy in livers which received only a supply of systemic blood, and that auxiliary transplanted livers do not undergo definite atrophy, especially in man,[4] when they are connected to the systemic circulation.[21] The experiments of Marchioro[12] clearly show this. This author performed a series of shunts leaving one-half of the liver with its splanchnic supply while bringing to the other half venous systemic blood at a physiological blood flow rate. Only the latter half atrophied. This is easily explained by the fact that one-half of the liver received all of the splanchnic blood and thus utilized the trophic element found therein; there was no recycling. On the contrary, an injured liver does not effectively utilize the trophic supply in the splanchnic blood, particularly since a porto-caval shunt is performed before an auxiliary transplantation. The transplanted liver connected to the systemic circulation is then in the best conditions possible for using this recycled trophic element in the peripheral blood.[7,20,21]

The pancreas, therefore, appears to be a trophic organ of major importance, since insulin may play a primary role, especially in view of the fact that it seems increasingly sure that the insulin secreted by the pancreas may be merely a pro-insulin transformed by the liver into active insulin. It remains to be determined whether other substances (glucagon),[14] a possible third pancreatic hormone[19] are also involved. Moreover, these results imply that a drop of more than 30% in the total hepatic blood flow is poorly tolerated by the liver. From a practical point of view, the perfecting of an original technique of auxiliary transplantation of the liver will permit us to confirm or disprove these encouraging results, which should find wide experimental use in cirrhosis of the liver.

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Clinical Results of Parietal Cell Vagotomy (Highly Selective Vagotomy) Two to Four Years After Operation

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In Leeds and Copenhagen 271 patients were treated electively for duodenal ulcer by parietal cell vagotomy without drainage between 1969 and 1972 inclusive, with no operative deaths. 108 patients have been followed up 2–4 years since operation. Gastric stasis necessitating re-operation occurred in only 2 cases. Gastric ulcer developed in 2 cases, and in 3 cases recurrence of the duodenal ulcer was suspected but was unconfirmed at re-operation. Uncontrolled comparison with the results of partial gastrectomy and of vagotomy with drainage, as performed at these two centers, has shown that after parietal cell vagotomy without drainage there is a much lower incidence of dumping, diarrhea and bile vomiting, and, on overall assessment, a greater proportion of perfect or very good results.

VAGOTOMY is at present performed at various levels. In truncal vagotomy (TV) the vagal trunks are isolated and cut on the oesophagus or at the cardia. Selective gastric vagotomy (SGV) involves the cutting of the anterior and posterior gastric nerves, leaving intact the posterior trunk with its coeliac branch and the anterior trunk with its hepatic branches. Most surgeons are in agreement about the necessity of adding a drainage procedure to these two types of vagotomy.

Alternatively, vagotomy can be performed at a more peripheral level, the gastric nerves of Latarjet[19] being preserved and only the small branches from these nerves being cut. By this technique various parts of the stomach can be denervated and the innervation of the remainder left intact. This principle was adopted in experimental animals by Griffith and Harkins[9] and used by Holle in clinical practice as Selektive proximale Vagotomie.[10] Holle denervated the upper part of the stomach and left the antral nerves intact, on the assumption that the vagus plays an important part in an antral inhibitory mechanism. He still claims that the stomach must be drained when this type of vagotomy is used.[11] However, experimental studies[1] showed that denervation of the acid-producing part of the stomach combined with preservation of antral innervation, did not result in significant alteration in gastric emptying. This vagotomy-without-drainage was used in clinical practice by Johnston and Wilkinson[14] in Leeds and Amdrup and Jensen[3] in Copenhagen. They termed these operations highly selective vagotomy (HSV) and parietal cell vagotomy (PCV) respectively. In this paper, the term parietal cell vagotomy (PCV) will be used to cover both HSV and PCV, because the difference in operative technique is small (*vide infra*). Both centers took up this operation in the hope that surgical cure of ulcer disease would be followed by fewer postcibal complaints, and both regard the avoidance of a drainage procedure as the crux of the matter in this surgical procedure.

Material

In the period 1969–1972 inclusive, 271 patients (59 females and 212 males) were operated on electively for duodenal ulcer in Leeds and Copenhagen. None of these patients had clinical symptoms of obstruction, food rem-

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TABLE 1. *Age at Operation*

Age	Number of Patients
Younger than 30	34
31–39	62
40–49	65
50–59	76
60–69	29
older than 70	5

271 patients operated on in Leeds and Copenhagen 1969–1972.

TABLE 3. *Preoperative Weight*

Preoperative Weight	Number of Patients
Less than 50 kg	16
50–59	56
60–69	87
70–79	66
80 kg or more	46

271 patients operated on in Leeds and Copenhagen.

nants in the fasting aspirates or radiological signs of gastric retention four hours after barium meal. No other form of selection was used with respect to age (Table 1), length of history (Table 2) or preoperative weight (Table 3) nor were the results of the preoperative acid secretion tests taken into consideration (Table 4). Half of the patient material in Copenhagen and approximately 30% in Leeds had previously had bleeding episodes or perforation.

Apart from the first year when a more hesitant policy was adopted in Copenhagen, the series represents a virtually consecutive study of elective operations. The pilot series have been followed in close co-operation between Leeds and Copenhagen. This paper gives the results especially those of followup of the patients treated 2–4 years ago.

Surgical Procedure

The surgical technique has been described previously.[3,14] In patients in Copenhagen and in some of the patients in Leeds the entire dissection is performed from the front, while in the majority of cases in Leeds the distal half of the posterior dissection is performed from behind after the stomach has been partially separated from the greater omentum and swung up. This difference in technique should be of no physiological importance. In Leeds the starting point of the dissection is determined by careful inspection of the vagal nerve fibres: the main nerves of Latarjet to the antral region are preserved, and all the other fibres passing to the stomach are severed. In Copenhagen, on the other hand, the boundary between the acid-secreting and the non-acid-secreting part of the stomach is determined by means of an intragastric pH-tube. As a result of this technical difference the length of the stomach left innervated in Leeds was 5–8 cm (mean, 6.5 cm) while the corresponding values for Copenhagen were 8–10 cm (mean, 9 cm). The pH-tube determination of the boundary was successful in 93 of 126 patients operated on in Copenhagen. In 24 patients the borderline could not be localized within a 1 cm movement of the pH-tube and was then defined by Congo Red staining of the mucous membrane through a gastrotomy. In nine cases, acid secretion could not be stimulated during operation, presumably because of atropinisation during induction of anesthesia, and anatomic landmarks were then used.

TABLE 2. *Length of History*

Length of History	Number of Patients
Less than one year	10
1–5 years	70
5–10 years	55
More than 10 years	136

271 patients operated on in Leeds and Copenhagen 1969–1972.

Early Postoperative Complications

None of the 271 patients died postoperatively. Two developed left subphrenic abscess which required drainage. Nineteen patients suffered wound infection of various degrees, which in 6 cases followed wound disruption. Two patients had thromboembolic complications.

Followup Examination

All patients operated on were invited to attend a special gastric followup clinic, and were reviewed at yearly intervals. Out of 183 patients operated on in 1969–1971 inclusive, one patient in Leeds had died from an accident and 6 patients in Leeds and 3 in Copenhagen could not be traced, leaving 93 patients who were re-examined in Leeds and 80 in Copenhagen. In total, 108 patients had been followed up for 2–4 years and 65 for 1–2 years. Assessment in Leeds was "blind," being made by a panel of three doctors who interviewed patients who had undergone all types of gastric surgery, ranging from simple suture of a perforated ulcer to radical gastrectomy for cancer.

TABLE 4. *Preoperative Pentagastrin-stimulated Peak Acid Output (PAO) (Unknown in 3 Patients)*

PAO (mEq/h)	Number of Patients
<20	10
20–29	45
30–39	76
40–49	60
50–59	49
60–69	18
>70	10

271 patients operated on in Leeds and Copenhagen.

No failure has yet been observed among patients operated on in 1972. In the following, poor results are given in relation to the number of patients treated more than one year ago while reference to alimentary dysfunction is restricted to the 108 patients with an observation period of more than two years.

Poor Results

Five of the 108 patients (4.6%) who were followed up for more than two years and eight of the 173 patients followed for more than one year (4.6%) had poor results (Visick grade IV). In two patients, one from each center, re-operation became necessary because of gastric stasis. In one of them the duodenal ulcer had healed but scarring had led to pyloric stenosis. In the other patient, no anatomical narrowing was found. No gastric ulcer was observed in either of these patients. Three patients underwent re-operation for ulcer symptoms which had aroused suspicion of an unhealed duodenal ulcer. No ulcer was found, however, and the complaints were little altered after the re-operation, which took the form of an antrectomy in two patients and a pyloroplasty in one patient. One patient in Leeds complained of persistent epigastric discomfort of moderate severity, but x-ray showed no stasis or ulcer and re-operation has not been performed. Two patients in Copenhagen had proven gastric ulcer. In one, stasis occurred after a period of normal gastric emptying, a positive insulin test changed to negative and the reduction in pentapeptide-stimulated acid secretion increased still further. At re-operation with antrectomy, the duodenal ulcer was found to have healed without stenosis but a gastric ulcer was observed on the lesser curvature. Some months later a bronchial carcinoma with huge mediastinal metastases was diagnosed. The other patient developed a radiologically- and endoscopically-proven gastric ulcer one year after operation during a period of intensive salicylate medication. The ulcer healed in response to non-surgical therapy but, like the other patients in this group, this patient has been graded Visick IV.

Dumping

At the time of discharge from hospital, the patients were advised to eat a full diet without restriction. The frequency of dumping which was recorded at followup is listed in Table 5. Only one of the 108 patients complained spontaneously of dumping. His preoperative record lists symptoms suggestive of dumping after intake of hypertonic liquids and he found that these complaints had increased after operation. Clinical dumping could not be provoked in this patient by oral intake of 150 ml of 50% glucose solution and radiological alterations characteristic of dumping[2] were not observed after the ingestion of a hypertonic barium meal. This patient also complained of diarrhea unrelated to meals and was placed in Visick grade III. When leading questions were used a further 5 patients had occasionally experienced slight and clinically unimportant symptoms of dumping. The total incidence of dumping was 5.6%.

TABLE 5. *Dumping Symptoms after PCV*

Intensity of Symptoms	Number of Patients	Per Cent
No complaints	102	94.4
Mild (non-spontaneous)	5	4.6
Moderate	0	0
Severe	1	1
Total with symptoms	6	5.6

108 patients 2–4 years after PCV.

Diarrhea

Diarrhea associated with dumping did not occur in any of the patients but one patient experienced diarrhea if he drank milk. A further 4 out of 108 patients had episodic diarrhea not related to meals. The episodes consisted of the passage of two to three loose or liquid stools a day, for one or two days, at intervals of one to three months. In one of the patients urgency gave the diarrhea some clinical importance, but the other patients did not regard the post-operative alteration in bowel habit as particularly troublesome. In summary, mild diarrhea was recorded in 4% of patients and diarrhea of moderate severity in 1%.

Overall Clinical Results

An overall assessment according to the Visick grading (27) of the 108 patients examined at 2–4 years is given in Table 6. Eighty-eight per cent were in grades I and II. Apart from the patients with severe dyspepsia mentioned above and apart from the occurrence of dumping and diarrhea, other symptoms of alimentary dysfunction, often slight and episodic, were disclosed at the interview. Their incidence 2–4 years after operation is given in Table 7. None of these symptoms was sufficiently severe to demand any active treatment. Radiological examination was not a routine part of the followup study but when barium meals were performed they showed normal gastric emptying through a normal or somewhat distorted duodenal bulb.

Epigastric fullness after the main meal of the day

TABLE 6. *Visick Grading*

Grading	Number of Patients	Per Cent
Perfect	71	65.8
Very good	24	22.2
Fair	8	7.4
Poor	5	4.6

108 patients 2–4 years after PCV.

TABLE 7. *Symptoms of Alimentary Dysfunction (Per Cent)*

	Leeds (n 60)	Copenhagen (n 48)
Bilious vomiting	2	2
Dumping	7	4
Diarrhea	3	6
Hypoglycemic symptoms	5	2
Heartburn	12	8
Nausea	8	8
Epigastric fullness	29	15
Food vomiting	3	7
Flatulence	17	?*

108 patients 2-4 years after PVC.
* Flatulence was not specially enquired about in Copenhagen.

occurred in 29% of patients in Leeds but only 15% of patients in Copenhagen. This difference was not, however, accompanied by any difference in the incidence of episodic food vomiting, on the contrary this occurred in 7% of Danish patients compared with 3% of the English patients.

Weight gain was recorded in 51% of the patients (25% more than 5 kg), weight loss in 14% (6% more than 5 kg). In 35% the weight was unchanged compared to preoperative values.

Discussion

Interest in vagotomy without drainage is increasing and this has prompted us to furnish an interim report on the results obtained in the first 271 patients treated by this operation. The comparisons which have been made between PCV on the one hand and truncal or selective vagotomy with drainage on the other must obviously be viewed with caution, since the study is retrospective and the patients were not allotted in a random manner to one or other of the three types of vagotomy. We firmly believe that the only way to secure a truly accurate comparison of the results of different operations for any particular condition is by means of a properly controlled clinical trial in which patients are randomly allocated to the operative methods being tried, the same surgeons are responsible for the performance of the operations, and the assessment of the state of the patients on followup is conducted by the same observers using a uniform set of criteria and preferably without knowing at the time of interview which operation had been used in an individual case. We are unable to report such a trial of parietal cell vagotomy from our own experience, but are glad to note that trials of this nature have been commenced in other centers.[5-7, 20,28] Meanwhile, we can record the results we have had with this operation for duodenal ulcer in consecutive series of patients treated by it in Copenhagen and Leeds during the past four years. We also make some comparisons between these results and those recorded at the same interval after other elective operations for duodenal ulcer in these two centers. We would emphasize that identical and extremely stringent criteria of assessment were employed throughout in the followup of all these cases.

A recent combined study on spontaneous, insulin- and pentapeptide-stimulated acid secretion after PCV in Leeds and Copenhagen showed no material difference in the factors investigated between patients operated on in the two centers.[16,17] The present study also shows a high degree of similarity between the clinical results. The most notable difference was the higher frequency of epigastric fullness occurring after the main meal of the day in Leeds, and this was the chief reason for the lower incidence of perfect Visick grade I results in the English series. We feel that the questioning of the patients was equally thorough in the two centers and that the difference in frequency of this symptom is probably real. It could perhaps be explained by the denervation of the stomach having been more extensive in Leeds than in Copenhagen or perhaps by the English main meal being heavier than the Danish. The latter explanation is supported by the fact that the occurrence of episodic food vomiting was no more frequent in the English patients than in the Danish, which implies that gastric stasis is unlikely to have been the cause of the increased incidence of epigastric fullness in the patients in Leeds. Whatever may be the explanation for this particular difference, the striking overall similarity of the clinical and secretory results in the two centers casts some doubt on the need for routine demonstration of the antrum-corpus boundary at the time of operation. Certainly, there seems little to be said in favor of adding a gastrotomy for purposes of Congo Red testing when the pH-tube does not work for some reason, and at present we do not recommend that this procedure should be performed as a matter of routine.

Scarring during the healing of the duodenal ulcer might have been expected to give rise to mechanical obstruction at the gastric outlet, but up to now this has only occurred in one patient in the present series. The second patient with stasis may have suffered inadvertent damage to his nerves of Latarjet at the time of operation. Bearing in mind Dragstedt and co-workers' early experiences with truncal vagotomy without drainage,[8] we were afraid to begin with that gastric ulceration might occur with sufficient frequency to invalidate the use of the new "vagotomy-without-drainage." However, only two gastric ulcers have been observed. The observation period is still too short for a final evaluation to be made but it is a promising sign that bad results up to now have become manifest within one year of the operation.

Nausea, flatulence, epigastric fullness, food vomiting and heartburn are symptoms which arouse suspicion of gastric retention. These symptoms were recorded, however, with similar or greater frequency in patients after truncal or selective vagotomy and drainage than in patients after PCV (Table 8). A recent 5-year followup

TABLE 8. *Comparison of Symptoms after HSV without a Drainage Procedure with those after Truncal or Selective Vagotomy with Drainage*
(Per Cent)

Symptoms	HSV/PCV No Drainage (n: 108 patients)	Truncal ± Sel. V + P/GJ (n: 439 patients)
Bilious vomiting	2	11
Early dumping	5	20
Diarrhea	5	19
Food vomiting	5	8
Flatulence	17	24
Heartburn	11	16
Nausea	8	23
Epigastric fullness	24	34
Hypoglycemic symptoms	4	6
Dysphagia	0	1

Combined Leeds plus Copenhagen data at two years, a non-random, uncontrolled comparison.

of patients treated by selective vagotomy and drainage in Copenhagen yielded results similar to those recorded two years after operation.[4] Thus, the clinical results, as well as studies of gastric emptying in patients after PCV[13,24,25,29] have provided no evidence that a drainage procedure is a necessary accompaniment of PCV.

Another question is whether anything has been gained by the avoidance of a drainage procedure. This can be answered in the affirmative. When dumping occurs it becomes manifest soon after operation and hence a long observation period is not necessary for the evaluation of the frequency of this complaint. The overall frequency of dumping in patients after PCV was 6%. This is significantly less (Table 9) than the incidences recorded in Copenhagen after selective vagotomy and drainage (39%) and partial gastrectomy (35%). In Leeds, also, it has been shown[12,13] both by clinical studies and by the provocation of dumping with hypertonic glucose that HSV is followed by much less dumping than that which follows truncal or selective vagotomy with drainage. Dumping after PCV was not only infrequent but was also very mild in degree (except in one patient). When one allows for the tendency for dumping to diminish with the passage of time, it would appear that dumping as a clinical problem can be virtually abolished by the use of PCV.

TABLE 9. Incidence of Dumping after Three Types of Operation for Duodenal Ulcer in Copenhagen
(Per Cent)

	PCV	Sel. Vag. + Drainage	Partial Gastrectomy (B-II)
Number of patients	48	110	101
	At 2–4 Years	At 2 Years	At 4–5 Years
None	96	61	65
Mild	2	26	27
Moderate	0	11	5
Severe	2	2	3
Total dumping	4%	39%	35%

A non-random, uncontrolled comparison.

TABLE 10. *Incidence of Diarrhea after Truncal, Selective and Highly Selective Vagotomy in Leeds*
(Per Cent)

	HSV	Truncal V + P	Truncal V + GJ	Bilat. Sel. V + P
Number of patients	60	158	110	61
	At 2 Years	At 2 Years	At 2 Years	At 2 Years
Mild or moderate	3	18	21	13
Severe	0	6	5	2
Total incidence	3%	24%	26%	15%

A non-random uncontrolled comparison.

Whether diarrhea after vagotomy and drainage is caused by one or other of the two components of the procedure, or by a combination of both, has not been established. The significantly lower incidence of diarrhea which was found after selective vagotomy with drainage compared with after truncal vagotomy with drainage in randomized studies[18,26] indicates that vagotomy of abdominal organs outside the stomach has something to do with the alteration in bowel habit. In parietal cell vagotomy without drainage, not only the extragastric but also the antral innervation is left intact. Another factor in the production of diarrhea is likely to be the "gastric incontinence" which McKelvey and his colleagues[22] noted after complete gastric vagotomy with a drainage procedure. According to these authors, diarrhea is due partly to very rapid gastrointestinal transit of liquids. Such abnormalities of gastric emptying are much less marked after PCV[7,12,21,25] and, as we have shown previously,[13,15] hypertonic glucose elicits diarrhea in only 13% of patients after PCV (HSV), compared with 60% of patients after truncal or selective vagotomy with a drainage procedure. In this study, diarrhea was recorded in 5% of patients after PCV, which is a much lower incidence than that previously observed in the two centers after vagotomy with drainage (Tables 10 and 11). De Miguel[23] records 40% diarrhea after truncal vagotomy and drainage, 18% after selective vagotomy and drainage and 8% after PCV.

PCV is a less extensive operation than other surgical procedures used for duodenal ulcer. It is not a difficult operation although it requires a careful and meticulous

TABLE 11. *Incidence of Diarrhea after Three Types of Operation for Duodenal Ulcer in Copenhagen*
(Per Cent)

	PCV	Selective V + P	Selective V + P	Billroth II Partial Gastrectomy
Numger of patients	48	110	100	101
	At 2 Years	At 2 Years	At 5 Years	At 4–5 Years
Mild or moderate	6	9	14	6
Severe	0	1	1	1
Total incidence	6%	10%	15%	7%

A non-random uncontrolled comparison.

technique. The risk of severe postoperative complications is small. Our experience with PCV over the past four and a half years permits the following conclusions: the incidence of dumping and diarrhea is less than that which follows partial gastrectomy or truncal or selective gastric vagotomy with drainage. Symptoms and signs of gastric retention have been no worse than those encountered after partial gastrectomy or vagotomy and drainage. Hence, there seems to be no reason for adding a drainage procedure.

So far, then, the clinical results of PCV are very encouraging. In particular, the new operation has achieved one of its principal objectives; that of lowering the incidence of side-effects such as dumping, bilious vomiting and diarrhea, without at the same time producing any increase in the incidence of gastric stasis. However, because of the brief period of followup, many uncertainties remain. For example, it is still an open question as to whether the antrum-corpus boundary should be "mapped" routinely or not. Again, while relief of ulcer pain has so far been achieved in 95% of patients, the incidence of recurrence might well increase with the passage of time. Finally, it is not clear whether PCV is an adequate operation for *all* patients with duodenal ulcer, or whether for some patients a more radical procedure is necessary. All that can be said at present is that the results which we have obtained so far do not suggest that such a "selective" policy is necessary, nor is it clear upon what criteria selection would be based. Longer followup of the patients in this pilot study, and the results of prospective random trials which are now in progress, should resolve these uncertainties.

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A Simplified Technique for Hepatic Resection:

The Crush Method

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A new technique of hepatic lobectomy with combined use of hepatic clamp and liver crush clamp is described. It is a simplification of the original finger fracture technique by using instruments instead of fingers for hepatic resection. It provides the unexperienced with a technique of hepatic resection done in the shortest possible time and in an almost bloodless field with safety. Since February 1973 the author has performed 5 hepatic resections with this crush method for primary liver cell carcinoma. The blood transfusion averaged 200 ml and the operation time averaged 1.5 hours. No complication or mortality was encountered and the patients were invariably discharged within 14 days after the operation.

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SINCE THE PROPOSAL of the finger fracture technique for hepatic lobectomy in 1954, the feasibility and reliability of this technique have been attested to in 104 cases[1,2] and has proved superior to the conventional "control method." By finger fracture technique, the friable liver tissue is fractured with fingers while isolating the resistant vascular and ductal structures intrahepatically. The cumbersome and potentially dangerous procedure of isolating hepatic artery, portal vein, hepatic duct and hepatic veins outside of the liver in "control method" is thus avoided and the operative procedure is simplified. However, there is some unnecessary bleeding from the resection line which makes the surgeons feel uneasy with the finger fracture technique, even though it takes only 10 to 15 minutes to complete the resection.

To obviate this shortcoming of the finger fracture technique, a special hepatic clamp was designed by the author in 1970. Application of the hepatic clamp prior to finger fracturing of the liver renders hepatic resection possible in an almost bloodless field.[3] Nevertheless, this improved method is still deemed by many as a complicated maneuver. Inserting the fingers into a vascular spongeorgan like the liver and searching the main intrahepatic vascular and ductal structures with fingers certainly cause a feeling of insecurity to the unexperienced who refrain from its wide application. Recently the author further simplified the finger fracture technique by devising a "crush method." Basically, the crush method is similar to the finger fracture technique in principle. The only difference is that instead of fracturing the liver tissue and isolating the unyielding vascular and ductal structure with fingers, a heavy crush clamp is used to crush the liver tissue and expose the vascular and ductal structures under direct vision. This new technique has been applied in 5 cases of primary liver cell carcinoma since February 1973, and has proven the best and most simplified method for hepatic lobectomy. The result and the method are reported in detail.

Instruments

Specially designed hepatic clamp and liver crush clamp are required. The hepatic clamp (T. Y. Lin's hepatic clamp) has been previously reported in detail.[4] The liver crush clamp is designed to crush liver tissue without damaging the vascular or ductal structures of the liver as shown in Fig. 1B. It is heavily constructed, with a smoothly surfaced lower blade and a upper blade engraved with small shallow longitudinal grooves. The margins of the blades are rounded.

The scissors, though not specific for hepatic resection,

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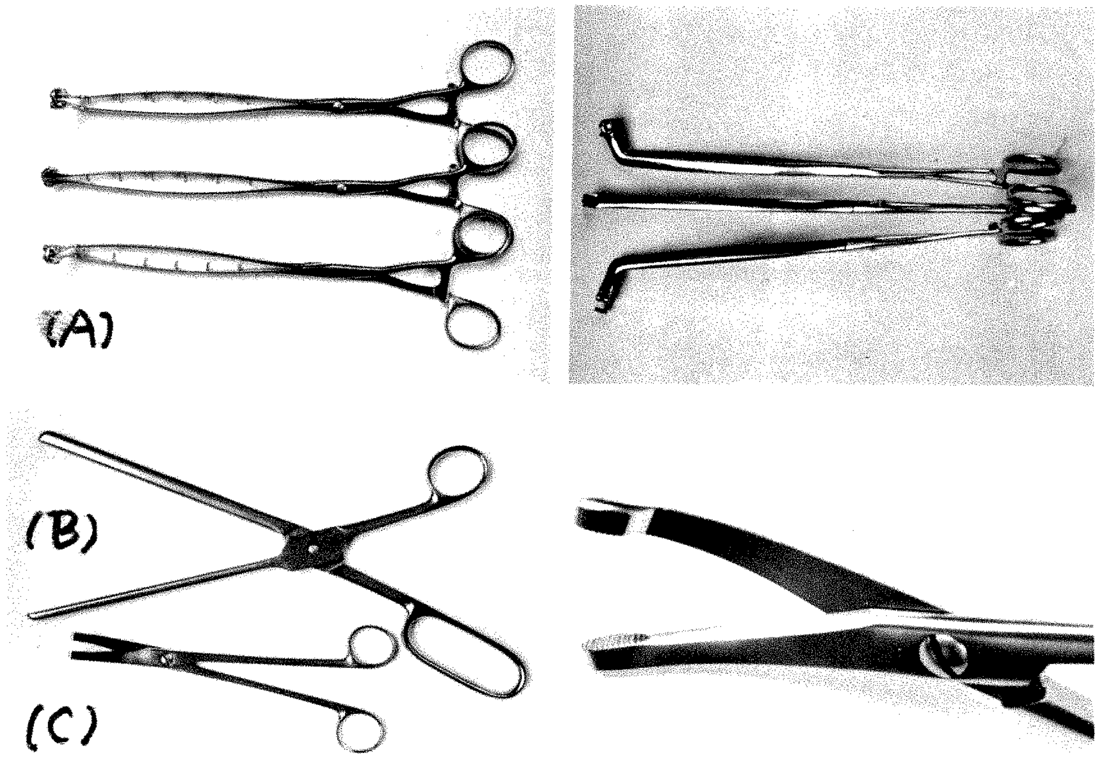

FIG. 1. T. Y. Lin's liver resection instrument. A. Hepatic clamp. B. Hepatic crush clamp. C. Scissors.

are made as shown in Fig. 1C. to serve triple roles as scratcher, guider and cutter.

Operative Technique

Hepatic Lobectomy

The upper abdomen is entered through a curved transverse incision along the costoabdominal line. Thoracotomy and splitting of diaphragm may be added if necessary. After exposing the lesion, the falciform ligament, triangular and the coronary ligaments of the affected lobe are divided and the liver is freed from the

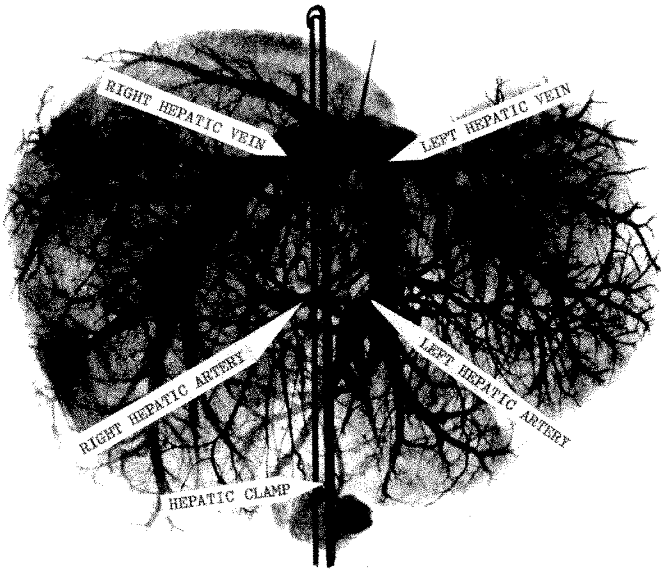

FIG. 2. The direction of hepatic clamp in relation to hepatic artery and hepatic vein in right hepatic lobectomy.

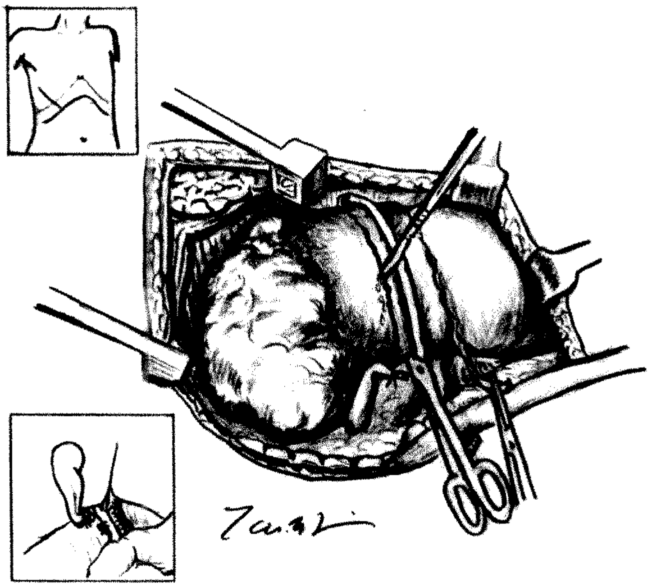

FIG. 3. Using the transected ligamentun teres for traction, the hepatic clamp is placed near the anatomical boundary of both lobes and the Glisson's capsule is now incised at the superior surface about 2.5–3 cm aside from the clamp.

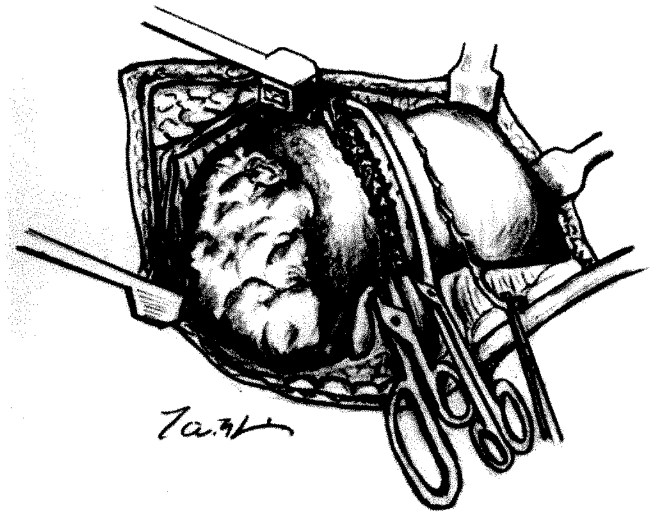

FIG. 4. Crush clamp is applied right on the incision line and thoroughly clamped to crush away the friable parenchymatous tissue.

diaphragm. In case of right hepatic lobectomy, the cystic duct and cystic artery are further cut, leaving the gallbladder attached to the right lobe. The end of the divided round ligament is clamped and used for traction to keep the liver in suitable position for resection. All these are needed before resection, leaving the hepatic artery, portal vein, hepatic duct and hepatic veins unexplored.

Next, the hepatic clamp is tightly applied on the affected lobe at the vicinity of the anatomical boundary of hepatic lobes, with the toothed blade on the superior surface (Figs. 2 and 3).

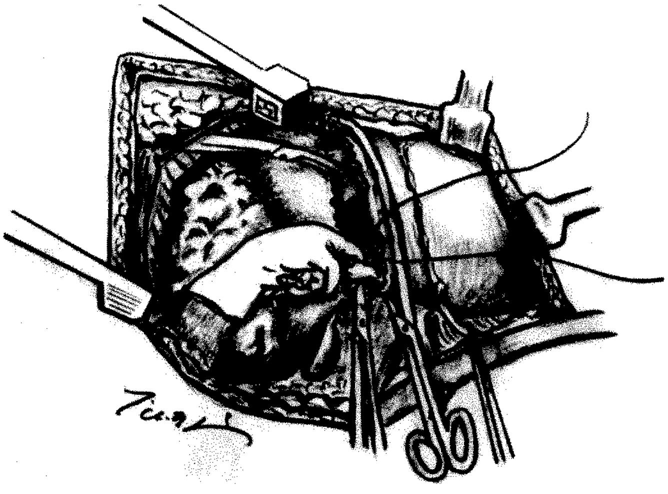

FIG. 5. On release of the crush clamp, the unyielding vascular and ductal structures appear as bridges between the two compartments of the liver. They are further isolated from the destroyed liver tissue with the finger and secured with double ligation followed by division to complete the hepatic lobectomy.

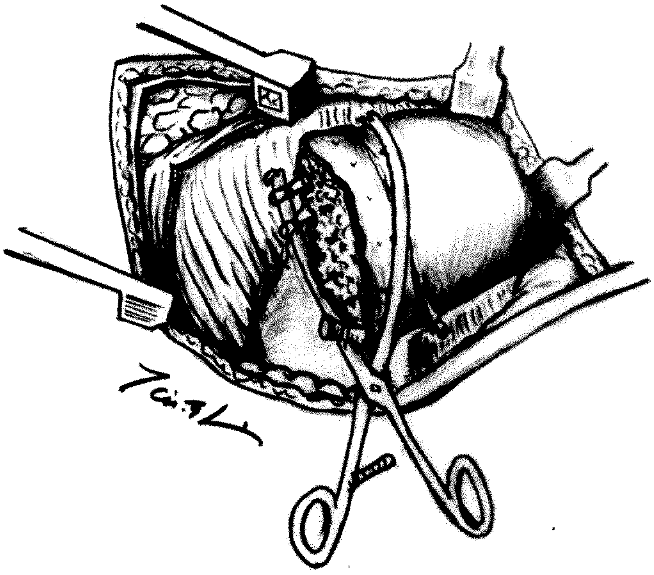

FIG. 6. After partial release of the hepatic clamp, bleeders from the liver parenchyma are suture ligated and then the clamp is removed.

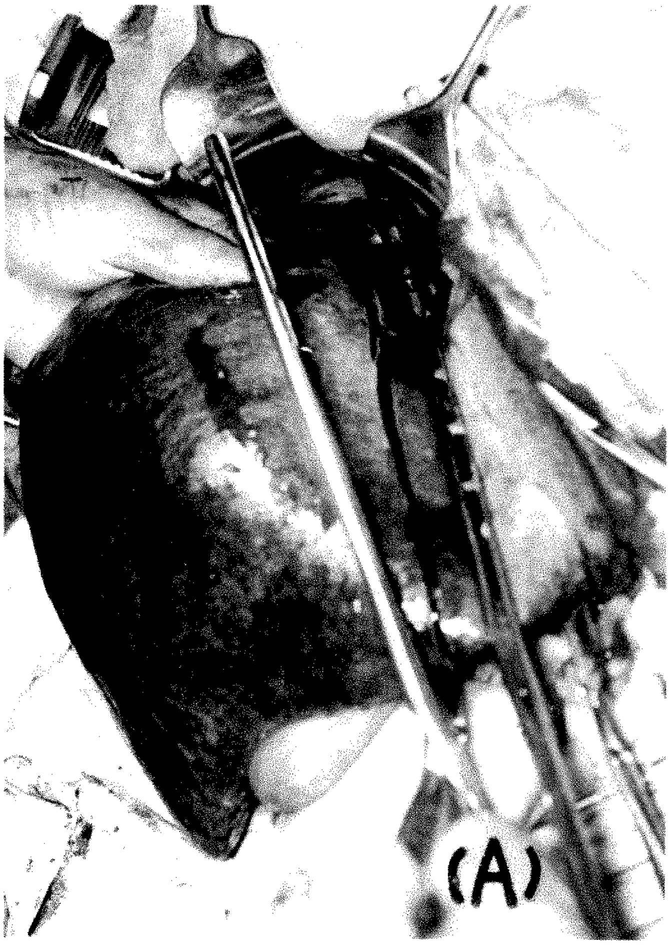

FIG. 7. A. Showing the incision line 2.5 cm aside from the applied hepatic clamp and the crush clamp about to be applied.

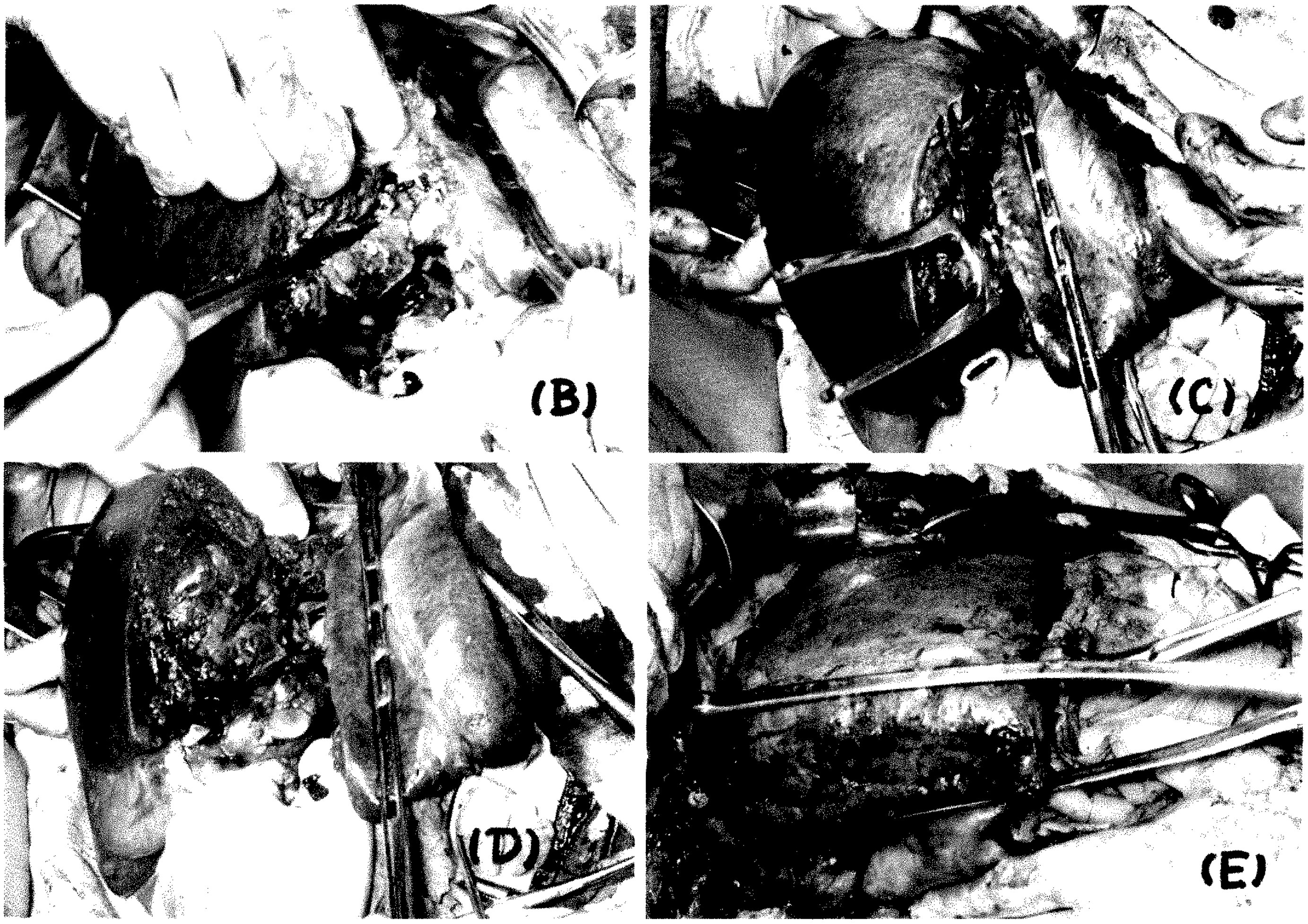

FIG. 7. B. After release of the crush clamp, the right hepatic artery, portal vein branch and right hepatic duct appear as whitish cords. C. Small crush clamp was reapplied to crush the posterior part of the liver which did not completely yield at the initial crushing. D. After thorough crushing, the hepatic vein now appears as a whitish cord at the posterior inferior aspect of the crush surface. E. After securing all of the bleeders by partial release of the hepatic clamp, the clamp is going to be removed.

A section line is created by cutting open the Glisson's capsule at 2.5–3.0 cm apart from the hepatic clamp on the superior hepatic surface of the affected lobe. (Fig. 7A). The rent so created on the liver capsule facilitates introduction of the crush clamp into the liver parenchyma. The crush clamp is now totally and tightly applied in order to crush away the liver tissue as that done by finger fracture (Fig. 4). The clamp is released and reapplied three times to break up all of the parenchymatous tissue. Great caution should be exerted in repeating the clamping and releasing in the same direction at the same plane with gentleness so that the unyielding ductal and vascular structures are not torn by traction or kinking.

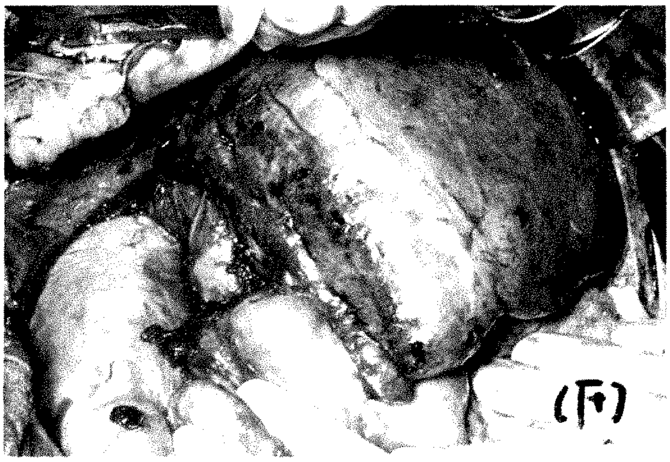

FIG. 7. F. Completion of right hepatic lobectomy.

The crush clamp is then removed. The crushed part of the liver looks like jelly and can be easily scraped off with the tip of T. Y. Lin's scissor to expose the ductal and vascular components which present themselves as whitish cords bridging the two compartments of the liver (Fig. 5). The hepatic artery, portal vein branches and hepatic duct lie anteriorly and the hepatic vein posteriorly at the crushed part of the liver. Smaller vessels and ducts are simply ligated, major ones are

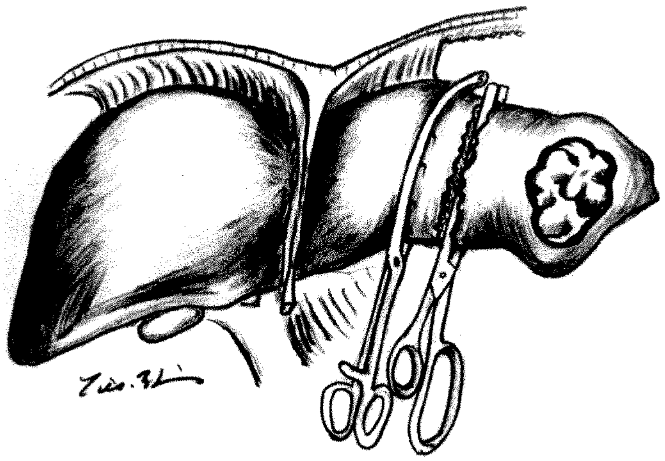

FIG. 8. The hepatic clamp in place. The liver parenchyma is crushed with the crush clamp through the incision on the superior surface of Glisson's capsule.

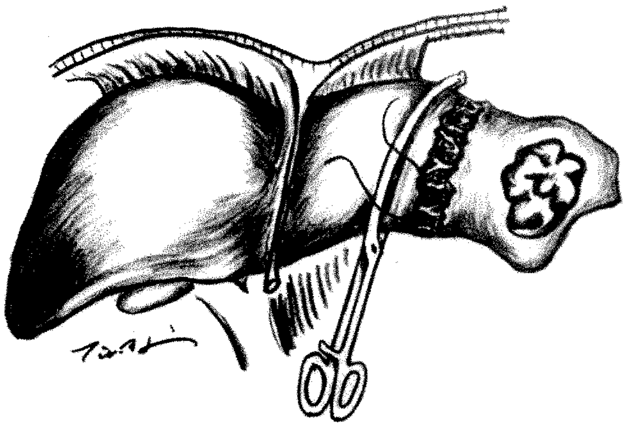

FIG. 9. On release of the crush clamp, the vascular and ductal structures remain as whitish cords bridging the two parts of the liver.

doubly ligated (with one being suture ligature) after securing its isolation with finger and rounding the ligating silk with the tip of the scissors. (Figs. 7B, D). These vascular and ductal components are then divided to detach the affected lobe.

The hepatic clamp is slightly loosened to check bleeders, and if any, they are suture ligated. The hepatic clamp is totally removed after complete hemostasis (Figs. 6, 7E).

The bare surface of the remaining liver is covered with nearly pedicle flap or free flap of omentum.

Partial Resection of the Liver

The hepatic clamp is applied at the healthy part of the affected lobe. A section line is created by cutting open the Glisson's capsule 2.0–2.5 cm apart from the hepatic clamp. The crush clamp is applied on the section line and crushes the liver tissue with force (Fig. 8).

On release of the crush clamp, the unyielding vascular and ductal components will appear as cord-like bridges connecting the two parts of the liver. These cord-like bridges are individually ligated and divided (Fig. 9).

The cut surface of the liver is secured of bleeding or bile leakage with interrupted mattress sutures.

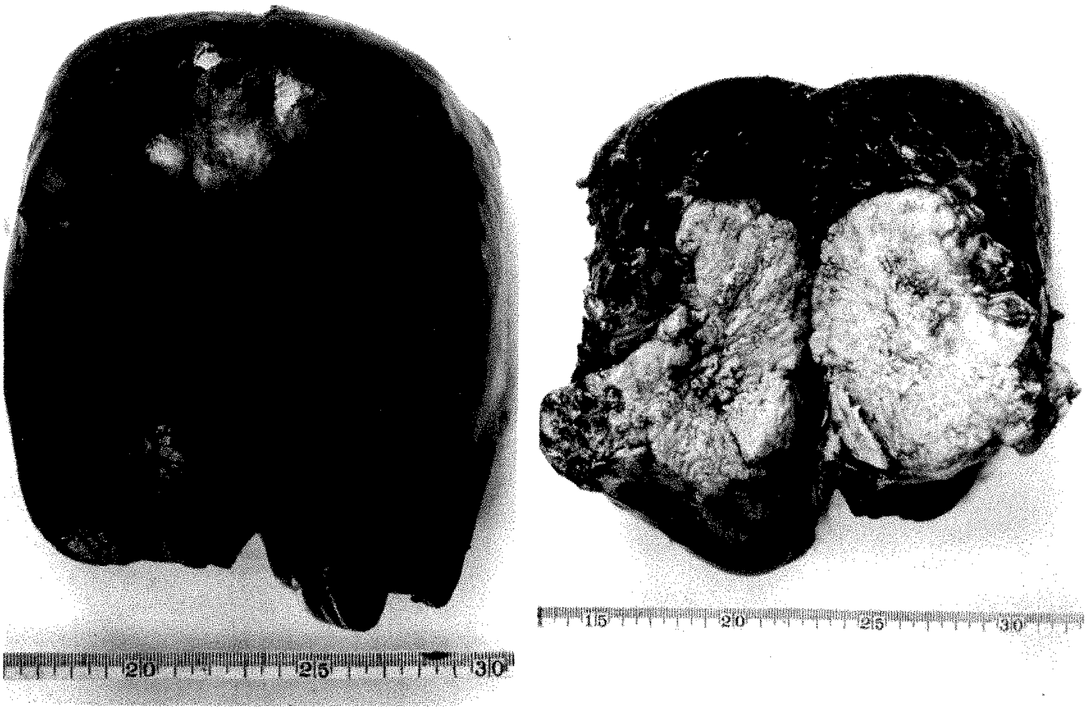

FIG. 10. Operative specimen showing malignant hepatoma.

TABLE 1. *Results of Author's Three Series of Hepatic Lobectomies*

Technique	Total Cases	Op. Time		Blood Transfusion	Operative Mortality
		Skin-to-skin	Liver Resection		
		(hrs)	(min)	(cc)	
Original Finger Fracture	104	2–3	10–15	1000–3000	3.8%
Finger Fracture + Hepatic Clamp	12	1.5–2.5	10	100–200	0%
Crush Method + Hepatic Clamp	5	1–2	5–8	100–200	0%

The hepatic clamp is then removed to complete the resection.

Results

Since February 1973, 5 cases of primary liver cell carcinoma were treated by hepatic lobectomy with this crush method. Of the 5 cases, 3 received right hepatic lobectomy and 2 had left hepatic lobectomy. One case that had undergone left lobectomy was associated with liver cirrhosis. The age varied from 32 years to 48 years and 3 were males and 2 females. The operation time needed with this method was about 1–1½ hours for skin to skin, and only about 5–8 minutes for hepatic resection per se. Blood transfusion during the operation amounted to less than 100 ml in all but two cases in which additional transfusion was needed for oozing in separating adherent mesocolon, colon, stomach and retroperitoneum from the tumor after completion of the hepatic resection. The resected hepatoma were all of massive type, weighing up to 2300 gm at maximum and some showed central necrosis (Fig. 10). Histologically they all proved to be liver cell carcinoma. None of the cases had postoperative complication and the patients were able to sit up by the third or fourth postoperative day and were discharged within two weeks after operation.

Discussion

The crush method is similar to the original finger fracture technique in principle and in shortening the operation time needed for hepatic resection by avoiding isolation and division of the hepatic artery, portal vein branches and hepatic duct at the hepatic hilum and hepatic veins underneath the diaphragm as that done in the "control method." The crush method is actually a simplified method of the original finger fracture technique and bears many advantages over the latter in that: 1) since a hepatic clamp is being applied at the anatomical boundary of the liver lobes before crushing the liver tissue, the fear of bleeding in the crush method is thus obviated and hepatic resection can be carried out in an almost bloodless field; and 2) the insecurity of the finger fracture technique in inserting a finger into a vascular spongeorgan like the liver and searching for vascular and ductal components with the inserted fingers is avoided in the crush method which presents the vascular and ductal structures to be divided readily under direct vision after crushing the liver tissue with crush clamp. The other benefit of the crush is that the presence of liver cirrhosis or fibrosis, which defies finger fracturing, will yield to the crush clamp.

The result of three series of patients treated with original finger fracture technique (104 cases between March 1954 and November 1970), with the hepatic clamp and finger fracture technique (12 cases between December 1970 and January 1973), and with the crush method and hepatic clamp are compared. The superiority of the crush method over the other two is evident from Table 1.

The only shortcoming of the crush method is that when the tumor extensively involves a whole hepatic lobe or more, there may be no room for applying either the hepatic clamp or crush clamp. In such instance, the original finger fracture technique may be resorted to for hepatic resection with the help of rapid transfusion with pumping system and transient occlusion of hepatic inflows at the hilum with the Satinsky vascular clamp.

References

1. Lin, T. Y., Hsu, K. Y., Hsieh, C. M. and Chen, C. S.: Study on Lobectomy of the Liver; A New Technical Suggestion on Hemihepatectomy and Reports of Three Cases of Primary Hepatoma Treated with Total Left Lobectomy of the Liver. J. Formosan Med. Assoc., **57**:742, 1958.
2. Lin, T. Y., Chen, K. M. and Liu, T. K.: Total Right Hepatic Lobectomy for Primary Hepatoma. Surgery, **48**:1048, 1960.
3. Lin, T. Y.: Results in 107 Hepatic Lobectomies with a Preliminary Report on the Use of a Clamp to Reduce Blood Loss. Ann. Surg., **177**:413, 1973.
4. Lin, T. Y.: New Hepatic Clamp. (Submitted to Ann. Surg.)

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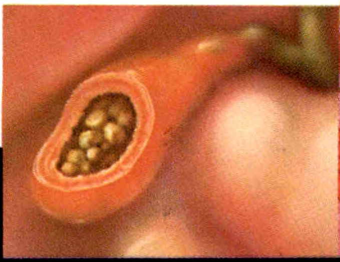
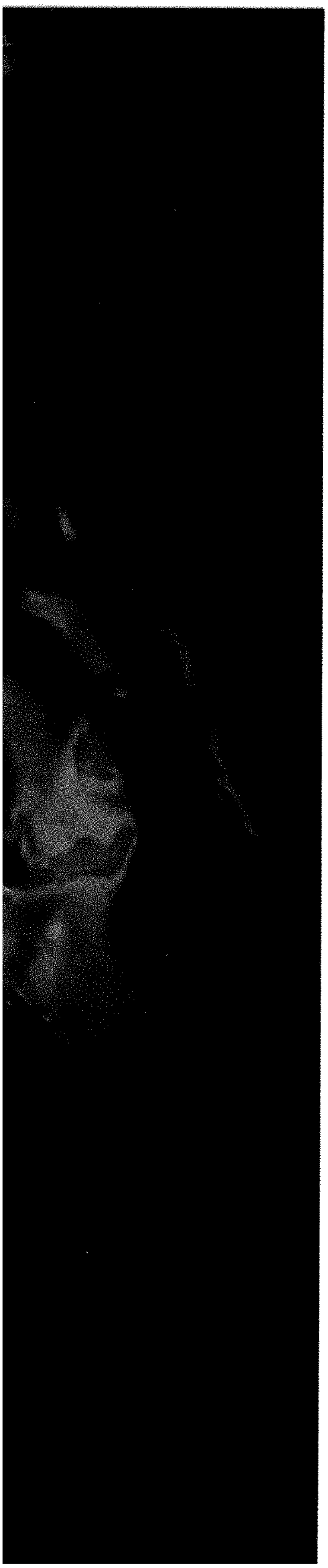


1. Artist's conception of cutaway view of gallbladder containing stones which, by causing irritation of the organ's interior wall and restricting biliary flow, may play a role in the repeated episodes of inflammation and infection associated with chronic cholecystitis.
2. Artist's conception of microscopic section of gallbladder wall showing chronic state with superimposition of inflammation, edema and necrosis due to an acute episode.

A unique view of the gallbladder, from the inside looking out,



Cholecystitis from the pathogen's point of view

Vibramycin (doxycycline) penetrates gallbladder tissue to reach susceptible[1] pathogens

Vibramycin can be useful in cholecystitis because it provides a wide antibacterial spectrum and therapeutic tissue concentrations.[2] Vibramycin is active against susceptible[1] strains of bacteria including Escherichia coli and Enterobacter aerogenes (formerly Aerobacter aerogenes).

Concentrations of oral Vibramycin in gallbladder tissue removed from four surgical patients on a dosage of 200 mg. P.O. stat and 100 mg. P.O. once daily until surgery.[2]

Patient No.	Concentration in Tissue (mcg./Gm.)
1	5.80[3]
2	1.58
3	8.68
4	7.73

---

[1] Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

[2] Fabre, J. et al.: Schweiz. Med. Wochenschr. 97:915, May 17, 1967.

[3] Concentration in the bile taken simultaneously: 24.2 mcg./ml.

Vibramycin® I.V.

(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.
200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid.

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See Brief Summary on following page for information on side effects and contraindications.

Penetrates tissue to reach susceptible* pathogens...

Vibramycin® I.V.

(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.
200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid.

Important facts about Vibramycin (doxycycline)

- can maintain therapeutic blood levels with a single daily infusion
- can be used without complexities of dosage alteration in patients with impaired renal function
- does not significantly elevate BUN in patients with renal insufficiency
- virtually the same broad range of indications when switching from I.V. to oral form

*Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

Vibramycin® Hyclate (doxycycline hyclate) and
Vibramycin® I.V. (doxycycline hyclate for injection)
BRIEF SUMMARY

Contraindicated: In persons hypersensitive to any of the tetracyclines.

Warnings: Use of tetracyclines during the last half of pregnancy, infancy and childhood to the age of 8 years may cause permanent discoloration of developing teeth. This is more common during long-term use of the tetracyclines but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Thus, tetracyclines should not be used in this age group unless other drugs are not likely to be effective or are contraindicated. Individuals receiving tetracycline antibiotics should be advised that direct sunlight or ultraviolet light can cause photosensitivity reactions. If these reactions (exaggerated sunburn) occur, discontinue therapy. Doxycycline forms a stable calcium complex in any bone-forming tissue. Fibula growth has been decreased in prematures given oral tetracyclines 25 mg./kg. q. 6 h., but this reaction was reversible when the drug was discontinued.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur to a significant degree with the use of Vibramycin in patients with impaired renal function.

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus. Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

Precautions: Overgrowth of nonsusceptible organisms may occur, including fungi. If such superinfections are encountered, discontinue Vibramycin and institute appropriate therapy.

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before initiating therapy. Conduct monthly serological tests for at least 4 months.

Because tetracyclines depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, conduct periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic.

Treat all Group A beta-hemolytic streptococcal infections for at least 10 days.

Avoid giving doxycycline with penicillin because of possible interference with penicillin activity.

Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given concomitantly to patients taking oral Vibramycin.

Adverse Reactions: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, maculopapular and erythematous rashes, exfoliative dermatitis, photosensitivity, urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. Prolonged administration of tetracyclines may produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Bulging fontanels have been reported in young infants on therapeutic dosage but disappeared when the drug was discontinued. A dose-related rise in BUN has been reported.

Oral Adult and Children's Dosages: See the Vibramycin Oral package insert for recommended dosage schedules for adults and children.

Intravenous Dosage and Administration: Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg./day) differs from that of the other tetracyclines (1-2 Gm./day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that Vibramycin, at the usual recommended doses, does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Intravenous Adult Dosage: The usual dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending on the severity of infection, with 200 mg. administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg. daily for at least 10 days.

Intravenous Children's Dosage: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg./lb. of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See "Warning" Section for Usage in Children.)

General: The duration of infusion may vary with the dose (100 to 200 mg. per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg. of a 0.5 mg./ml. solution is one hour. Desired concentrations of the final solution should be 0.2 mg./ml. to 0.5 mg./ml. Concentrations below 0.1 mg./ml. or above 1.0 mg./ml. are not recommended. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly nor subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

More detailed professional information available on request.

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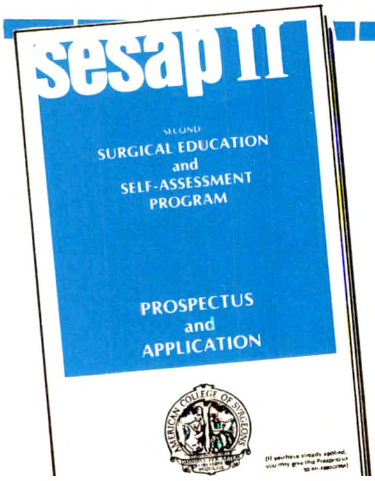
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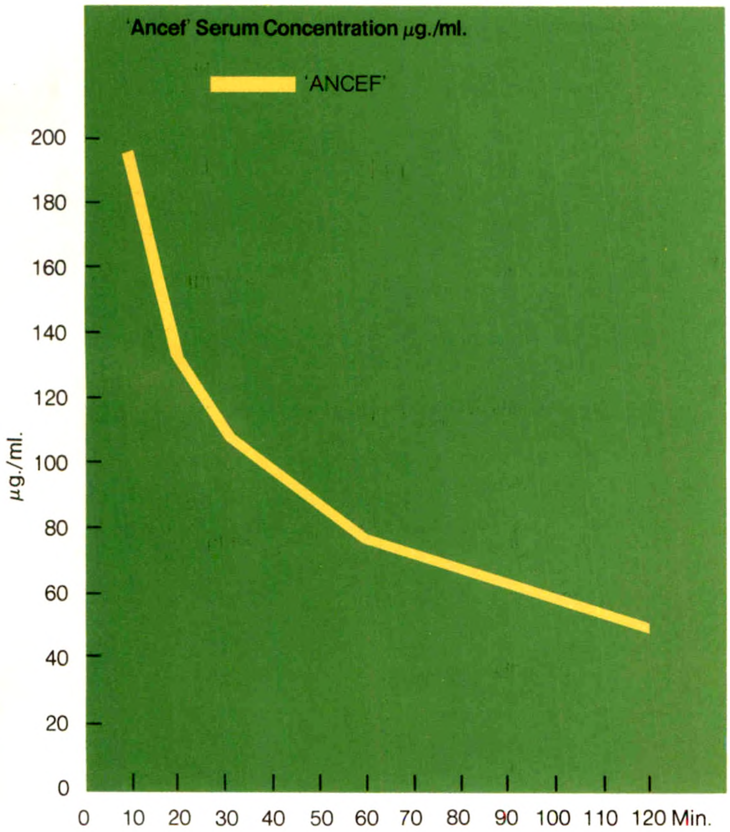

Average Serum Concentration of 'Ancef' following a single 1 gram I.V. injection. (Study conducted in 20 healthy adult volunteers.)

'ANCEF' Indications

Respiratory tract infections due to *D. pneumoniae, Klebsiella* species, *H. influenzae, S. aureus* and group A beta-hemolytic streptococci.

Genitourinary tract infections due to *E. coli, P. mirabilis, Klebsiella* species and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *S. aureus*, group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *S. aureus*.

Septicemia due to *D. pneumoniae, S. aureus, P. mirabilis, E. coli* and *Klebsiella* species.

Endocarditis due to *S. aureus* and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

'ANCEF' I.V. has a low risk of phlebitis at the injection site.

Duration of I.V. Therapy	Number of Patients	Average Daily Dose	Number with Phlebitis
1 day or less	13	3.0 g.	1
2 days	43	2.6 g.	1
3 days	31	3.3 g.	1
4 days	19	2.6 g.	1
5 days	37	2.6 g.	1
6 days	26	4.7 g.	0
7 days	26	3.8 g.	0
8 days	17	3.0 g.	0
9 days	11	3.1 g.	0
10 days	6	2.7 g.	0
More than 10 days	44	4.9 g.	1
Total	273	3.4 g.	6 (2.2%)

Of 273 patients receiving 'Ancef' intravenously, 6 patients or 2.2% reported phlebitis at the injection site. As can be seen in the above chart, which presents the duration of I.V. therapy, average daily dose and the occurrence of phlebitis, most cases of phlebitis occurred in the first few days of therapy which may be indicative that the inflammation was caused by the mechanical trauma of setting up the I.V. rather than continuing irritation of the drug itself.
These data were derived from pre-marketing clinical studies in small populations. Further clinical experience may reveal a greater incidence of adverse effects.

Pain on injection is infrequent with 'Ancef'.

ANCEF® Has Produced No Nephrotoxicity in Extensive Clinical Trials.

(Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.)

Adverse Reactions.

Adverse reactions reported in the clinical trials included: pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of adverse reactions associated with 'Ancef' therapy, please see brief summary of prescribing information on next page.

See following page for a brief summary of prescribing information including contraindications, warnings, precautions and dosage.

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ANCEF®

brand of

STERILE CEFAZOLIN SODIUM

(lyophilized)

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis.

'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Diplococcus pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus*.

Septicemia due to *Diplococcus pneumoniae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'ANCEF' IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for mild gram-positive infections is 250 mg. to 500 mg. of 'Ancef' every 8 hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every 8 hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 gram of 'Ancef' every 6 to 8 hours. 'Ancef' has been administered in dosages of six grams per day in serious infections such as endocarditis. 'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.) 60% of the normal daily dose given in divided doses q12h should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.) 25% of the normal daily dose given in divided doses q12h should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.) 10% of the normal daily dose given q24h should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dose may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories, Division of SmithKline Corp.,
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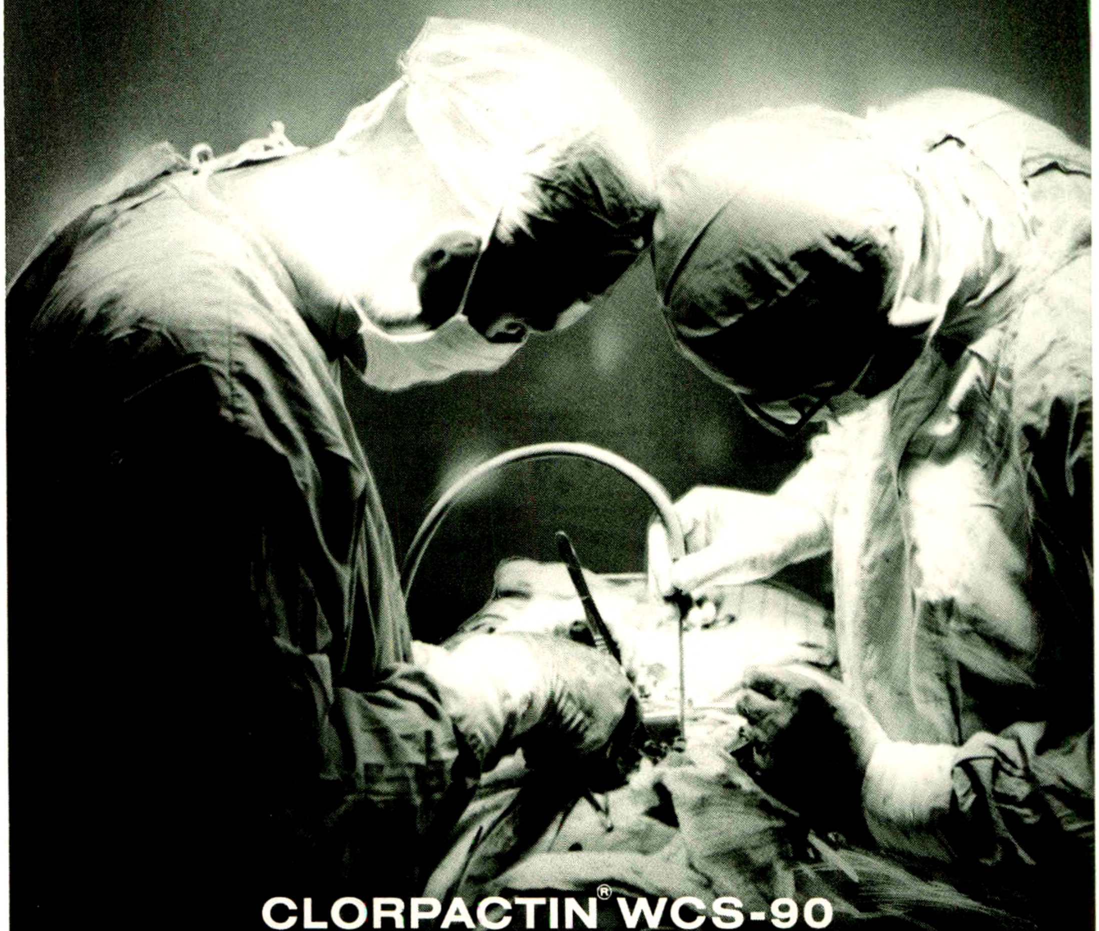

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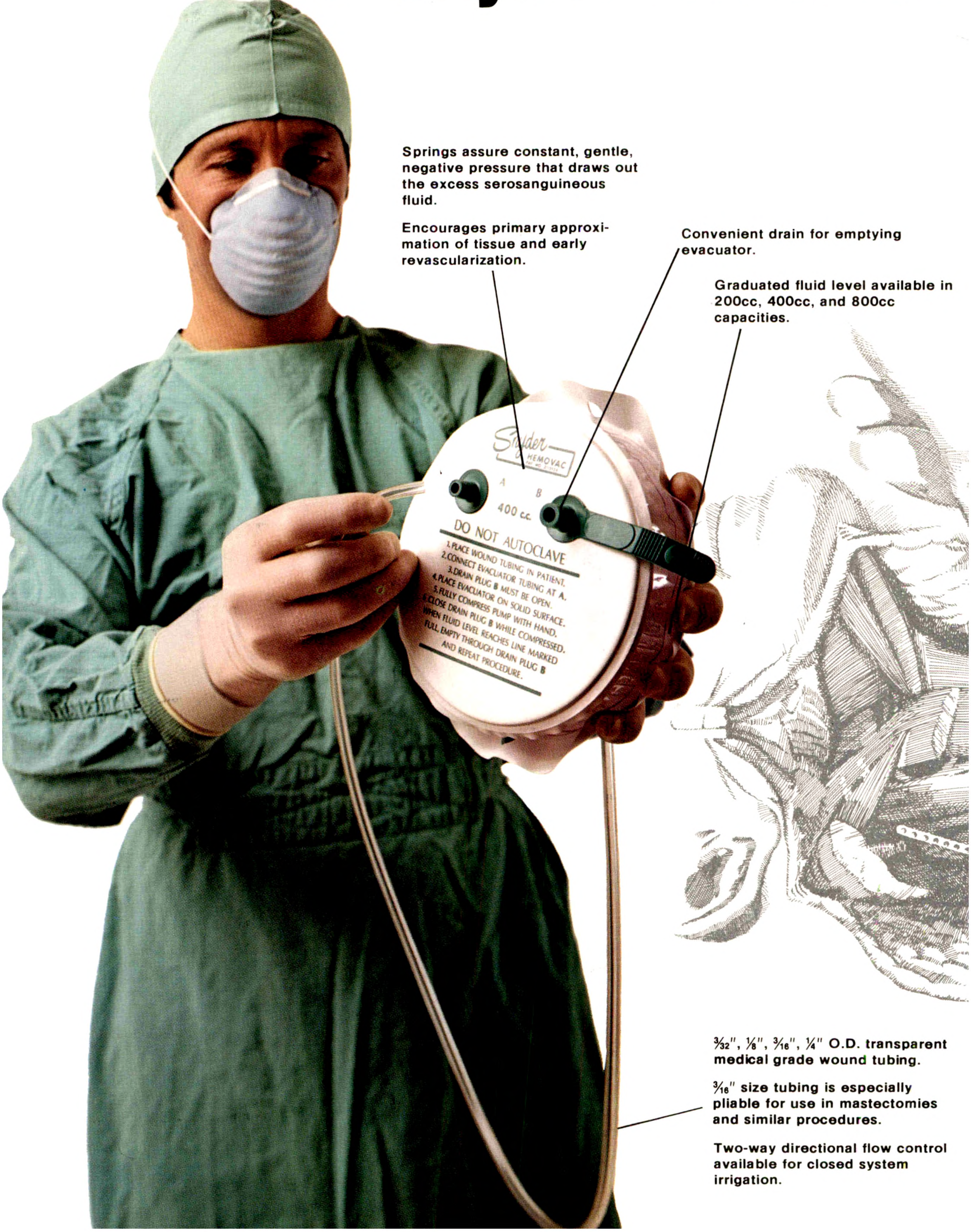
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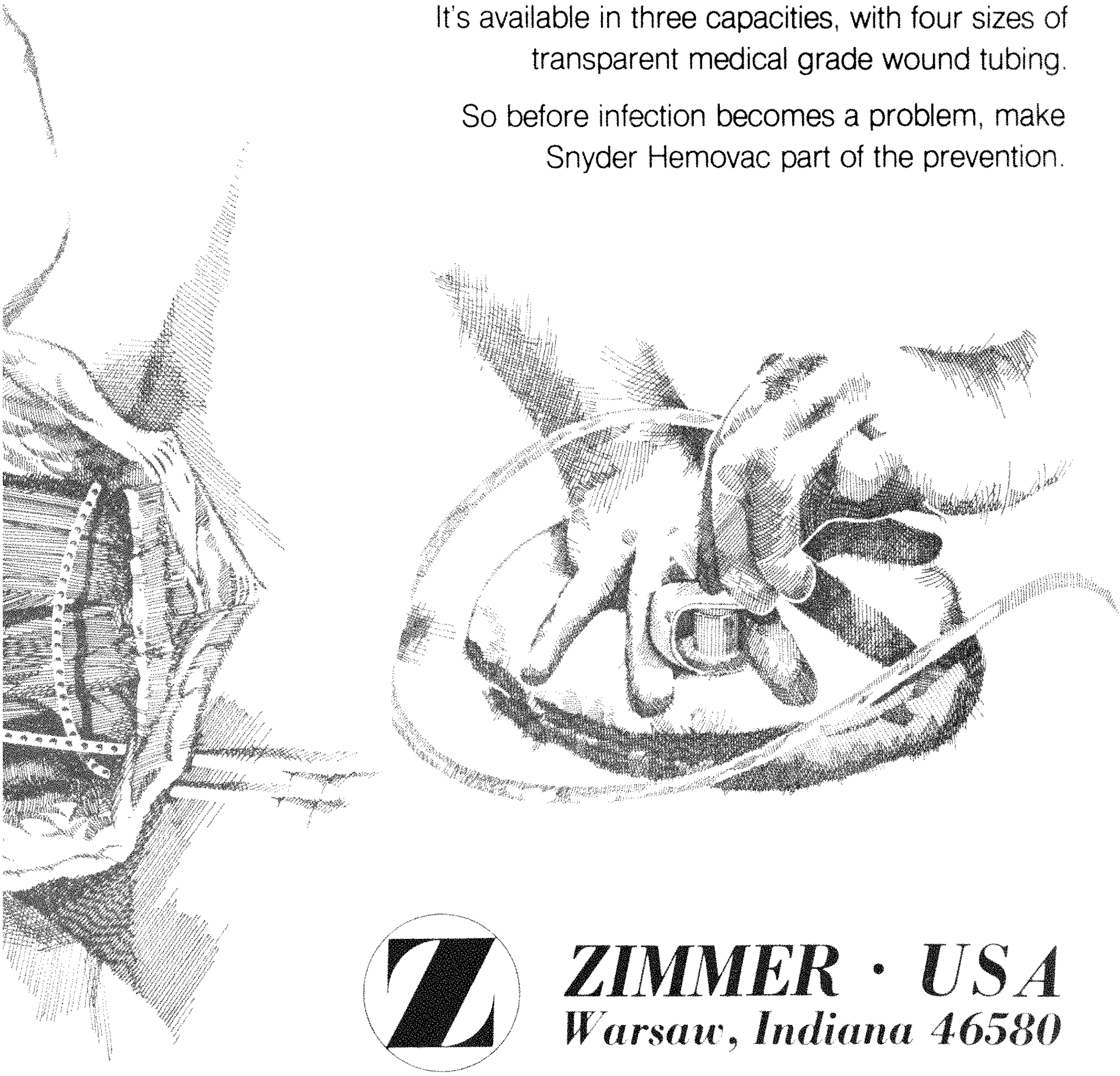

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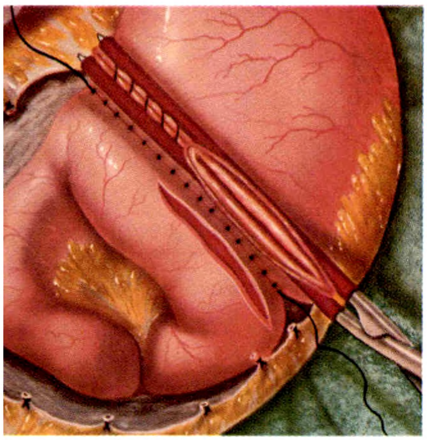
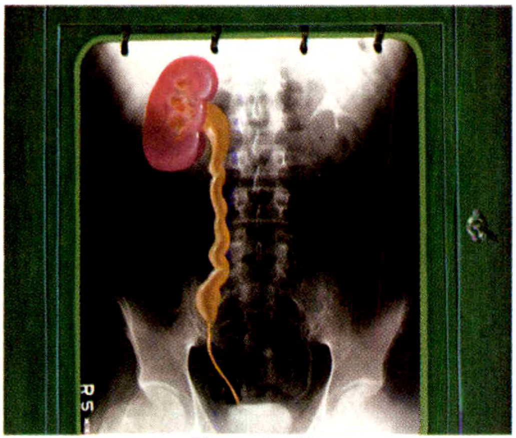

Gastrectomy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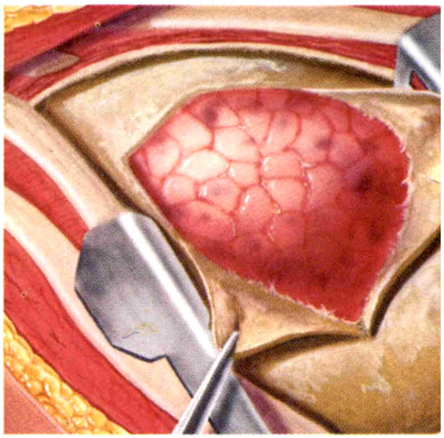
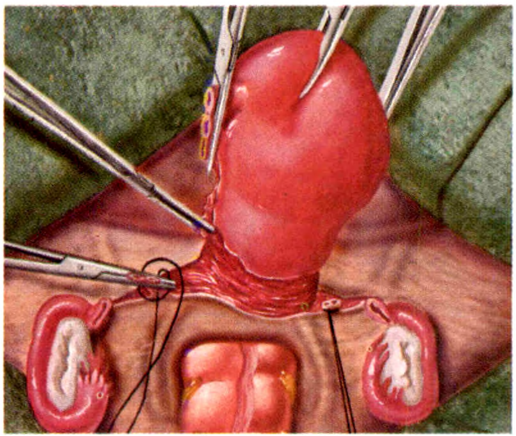
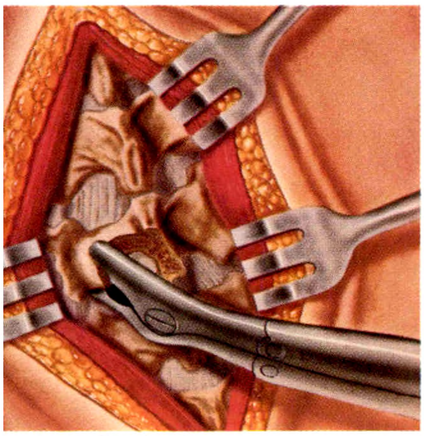

Thoracic surgery

Traumatic pain


Hysterectomy

Endoscopy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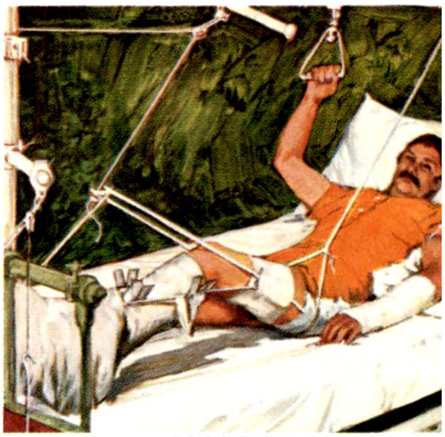
Burns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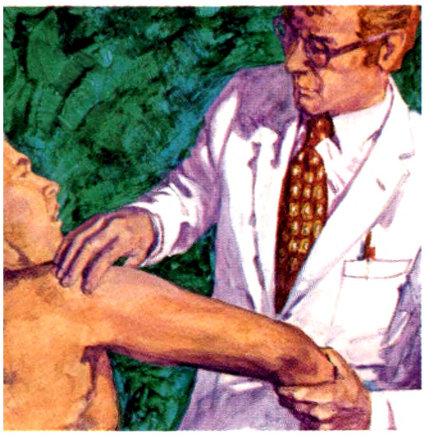
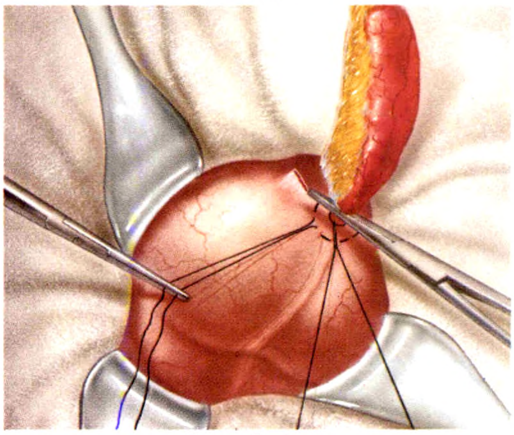
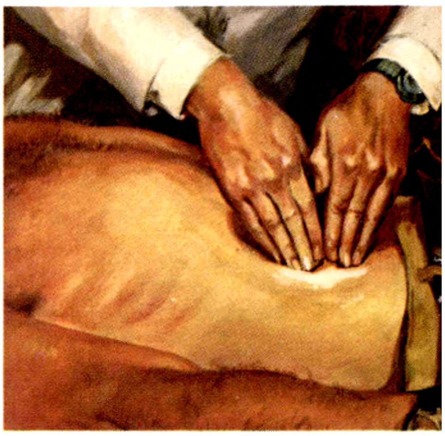

Acute bursitis


Appendectomy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Since clinical experience in children under 12 years of age is limited, the use of Talwin (brand of pentazocine, as lactate) in this age group is not recommended. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. See full instructions and warnings on last page.

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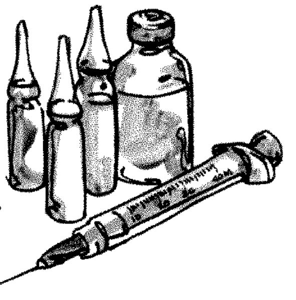

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Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; *dermatologic:* soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

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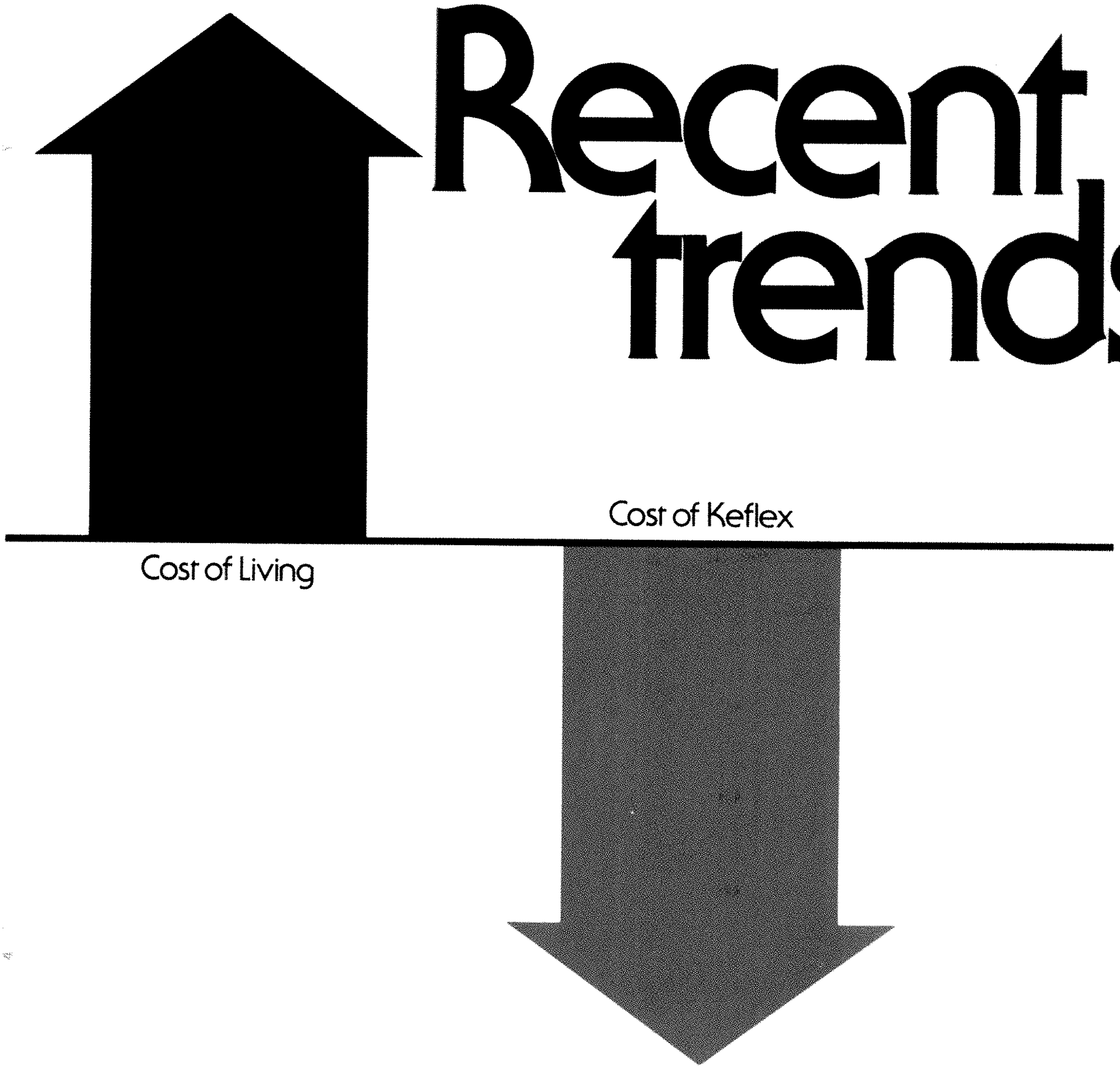

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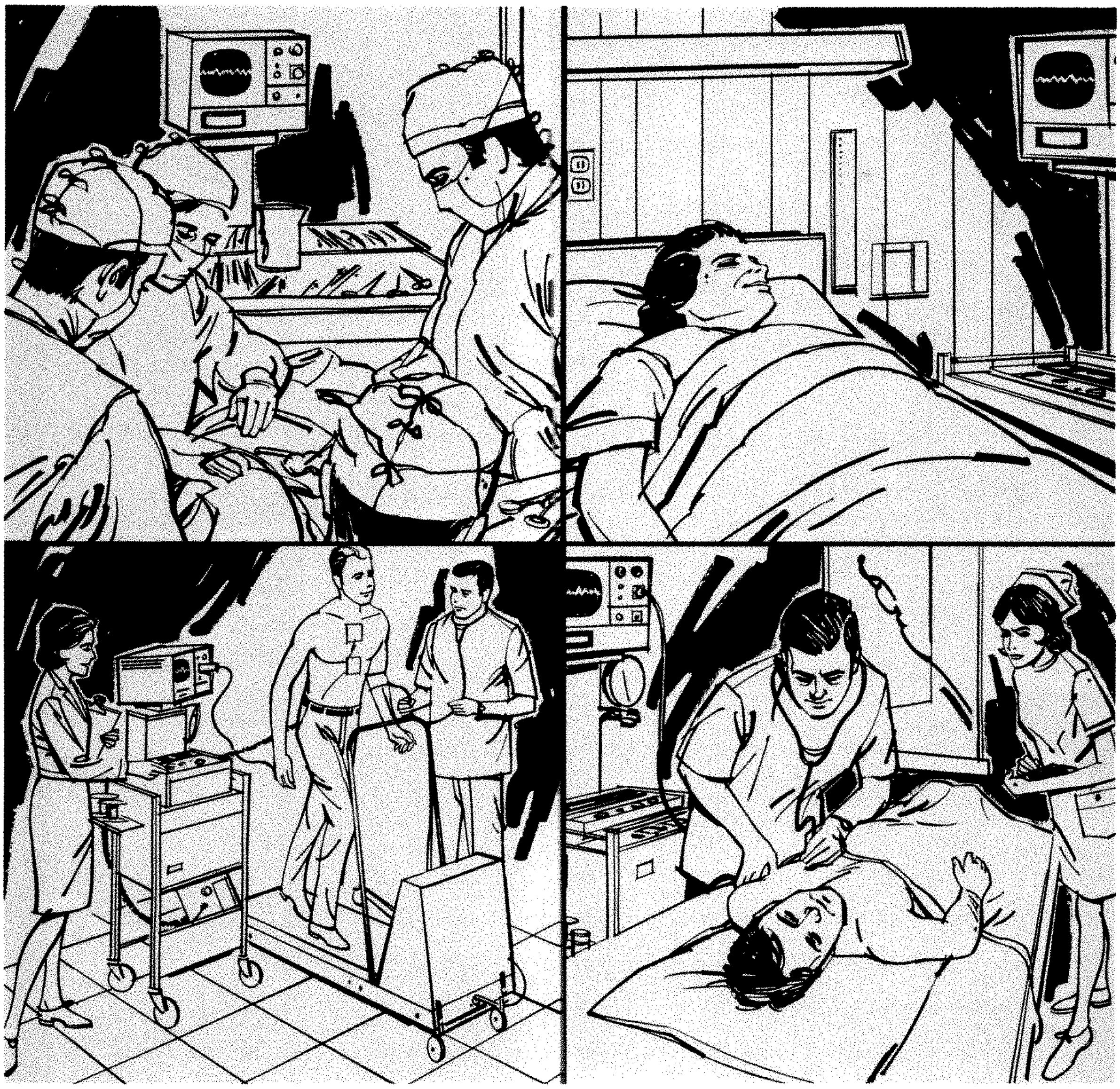

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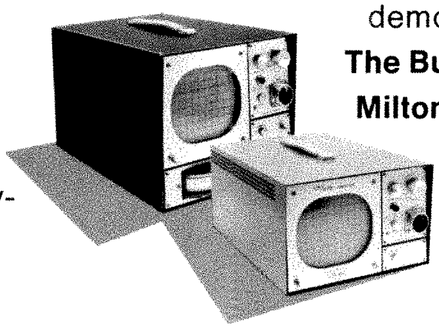

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Experience with the Modified Bovine Arterial Heterograft in Peripheral Vascular Reconstruction and Vascular Access for Hemodialysis

MOSHE HAIMOV, M.D., F.A.C.S.,* JULIUS H. JACOBSON II, M.D., F.A.C.S.†

From the Department of Surgery, Division of Vascular Surgery, The Mount Sinai School of Medicine of the City University of New York, New York, New York

The experience in the use of 37 Bovine heterografts for the treatment of arterial insufficiency and of 37 Bovine heterografts for construction of arterio-venous fistulas for hemodialysis is described. The Bovine heterograft was found unsuitable for use in the femoro-popliteal position, as contrasted to satisfactory follow-up in the aorto-iliac-femoral area. On the other hand, it was found to be an acceptable substitute to the autogenous saphenous vein in the construction of an arterio-venous fistula for chronic dialysis.

THE FIRST REPORT of the use of modified Bovine carotid arteries as vascular substitutes in the dog was published in 1956.[10] The first implantation in man was done six years later.[11] According to a recent editorial, over 3,000 grafts are currently in patients or in the hands of vascular surgeons.[12] With the exception of several favorable clinical reports,[2,9,13] the results from the use of all these grafts have not been reported. This report will deal with the experience with this prosthesis in a group of patients with peripheral vascular occlusive disease, and its use as a substitute for the autogenous saphenous vein in the construction of arterio-venous fistulas for hemodialysis in a second group of patients with terminal renal failure.

Materials and Methods

The Bovine arterial heterograft (Johnson and Johnson, Inc., New Brunswick, N. J.) is a tube prepared from the carotid artery of cows which has had the musculo-elastic tissue removed by the enzyme ficin. The remaining tissue consists of at least 76% collagen and is tanned with dialydehyde starch. The grafts are up to 50 cm long and 7½–14 mm in diameter. Antigenicity of the graft has not been demonstrated.[3] Histologic studies of these grafts implanted in dogs and in man has demonstrated that there are non-living substitutes for arteries. The late histologic reaction observed was one of fibrous invasion, substitution and integration.[4]

During a three-year period, 1966–1969, 37 Bovine heterografts were inserted in 32 patients. The indication for surgery were severe incapacitating claudication, rest pain and impending or limited gangrene. Patient age varied between 42 and 80. They all exhibited various degrees of generalized arteriosclerosis affecting the coronary and cerebral vasculature. The indication for the use of the modified Bovine heterograft were the unavailability or unsuitability of the long saphenous vein which was usually the prosthesis of choice. In all, there were 32 femoro-popliteal bypasses; two ilio-femoral bypasses; one aorto-femoral; one femoro-femoral; and one popliteal artery substitution following excision of popliteal aneurysm.

Thirty-seven Bovine heterografts were used in 31 patients with terminal renal failure in the construction of subcutaneous arterio-venous fistula for hemodialysis. Four patients had a loop fistula in the forearm (Fig. 1); 19 grafts were put in a straight fashion between the radial or ulnar artery and the antecubital or deep vein in the forearm; 14 heterografts were implanted in the arm as an A–V fistula between the brachial artery and the axillary vein. Indication for the procedure were

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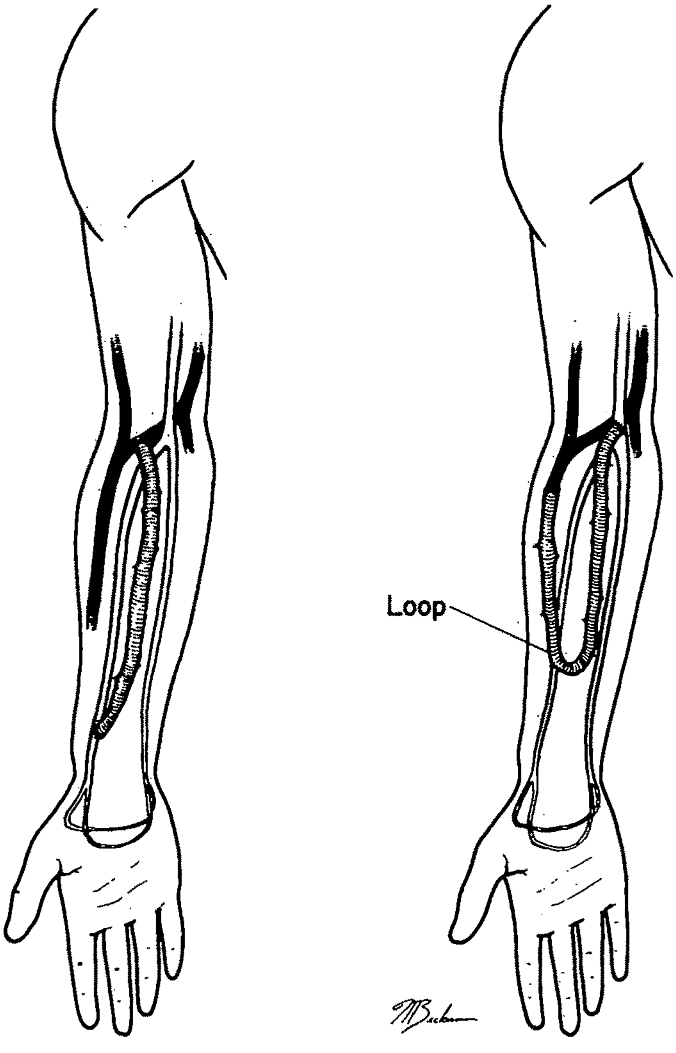

Fig. 1. Straight and loop heterograft A–V fistulas in the forearm.

Table 1. *Femoro-Popliteal Bypasses*
(32 Heterografts in 27 Patients)

Months Postop.	2	12	24–48
No. Open	20*	6	6
No. Closed	12	10†	10

* Includes 5 grafts which thrombosed postoperatively, but were successfully declotted.

† Three patients (4 grafts) died during the first year from unrelated causes.

unavailability of suitable artery or vein in the upper extremity for the construction of the standard subcutaneous arterio-venous fistula which is the vascular access of choice for hemodialysis. More than 50% of these patients were diabetic and many have had numerous vascular access procedures previously. No anticoagulants were used. All surgical procedures were done on an ambulatory basis using local infiltration anesthesia.

Results

Femora-Popliteal Bypasses (Table 1)

Of the 32 heterografts used in the femoro-popliteal location, 12 (38%) failed in the immediate postoperative period; 10 additional grafts failed during the first year of followup, six of them less than six months following surgery and six grafts (18% of the total or 38% if patient mortality is excluded) are patent for two to four years following implantation. Seventeen heterografts thrombosed in the immediate postoperative period and thrombectomy was done in 13 of them. In five, circulation was successfully restored, but the rest rethrombosed shortly thereafter. The clinical course and outcome of these 12

Table 2. *Femoro-Popliteal Bypasses Early Failures*

No.	Patient	No. of Grafts	Clinical Course and Outcome	No. of Operations
1	F. A.	1	Heterograft thrombosed postop. Thrombectomy unsuccessful. Peroneal artery injury with Fogarty catheter. Femoral endarterectomy performed. Groin infection .Expired.	3
2	F. B.	2	Graft degeneration with aneurysm formation, not at suture lines. New heterograft inserted which thrombosed postop. Thrombectomy attempted twice unsuccessfully. Limb viability preserved.	3
3	M. R.	1	Graft thrombosed in the early postop. course. False aneurysm developed with proteus sepsis. Graft removed.	3
4	C. S.	1	Early thrombosis postop. Circulation restored with thrombectomy. Aneurysmal degeneration of graft occurred necessitating graft ligation.	3
5	M. L.	1	Groin infection with massive bleeding. Expired.	2
6	T. M.	1	Massive bleeding from groin suture line .Expired.	1
7	J. R.	1	Early graft thrombosis. Thrombectomy. Acute myocardial infarction. Expired.	2
8	B. F.	1	Graft thrombosed. Thrombectomy unsuccessful. Arm vein graft also thrombosed. Above-knee amputation. Acute myocardial infarction. Expired.	4
9	C. G.	1	Graft thrombosed. Thrombectomy unsuccessful. A-K amputation.	3
10	B. I.	1	Graft thrombosed in one week. Limb remained viable.	1
11	W. R.	1	Graft thrombosed postop. Thrombectomy attempted twice without final success. A-K amputation.	4

TABLE 3. *Femoro-Popliteal Bypasses*
(2–48 Month Followup)

No.	Patient	No. of Grafts	Clinical Course and Outcome	No. of Operations
1	I. S.	2	Bilateral femoro-popliteal bypass (not simultaneous). One graft thrombosed postop., but was sucessfully declotted. Died after 12 months from myocardial infarction.	3
2	D. J.	1	Graft thrombosis postop. but was sucessfully declotted. Died after 6 months from mesenteric thrombosis.	2
3	M. M.	1	Graft thrombosed postop.—declotted. thrombosed again in 3 months. Above-knee amputation.	3
4	S. J.	2	Bilateral femoro-popliteal bypass. One graft thrombosed in 5 months. Two attempts of thrombectomy failed and A-K amputation was done. Second graft remained open for 9 months. Patient died from cerebrovascular accident.	5
5	R. J.	2	Graft removed because of false aneurysm formation after 3 months. Second heterograft failed (2 thrombectomies). A-K amputation.	4
6	H. L.	1	Graft thrombosed postop. Thrombectomy sucessful in restoring circulation. Graft thrombosed after 5 months.	2
7	R. K.	1	Graft thrombosed in 3 months.	1
8	F. B.	2	Bilateral femoro-popliteal bypass. Both grafts thrombosed within 6 months.	2
9	F. R.	1	Graft thrombosed in 5 months.	1
10	M. P.	1	Graft thrombosed postop. Thrombectomy successful. Thrombosed again in 8 months, this time thrombectomy failed.	3
11	S. I.	1	Graft remained open for 3 years, when patient died from myocardial infarction.	1
12	E. M.	1	Open for 2 years. Patient died following acute myocardial infarction.	1
13	B. S.	1	Graft open for 4 years.	1
14	B. M.	1	Graft open for 2 years.	1
15	W. V.	1	Graft open for 4 years.	1
16	M.G.	1	Graft open for 2 years.	1

failed heterografts in 11 patients are summarized in Table 2.

Ten grafts in 10 patients thrombosed luring the first year of followup (thrombectomy was attempted and was unsuccessful in seven of these patients). Two patients expired, six and nine months following graft implantation with open grafts for unrelated reasons. One patient died from mesenteric thrombosis and a second one following a cerebro-vascular accident. Three patients underwent major amputations following failures of the grafts and in five patients the viability of the extremity was preserved despite the graft failure. Clinical course and outcome of these patients is summarized in Table 3. In six patients the grafts have remained open for two to four years.

Six heterografts were implanted in other than the femoropopliteal location (Table 4). Only one of these grafts has failed (that was an ilio-femoral bypass in a young patient with severe large and small vessel disease which closed three months following implantation). The rest have all remained open for 24 to 36 months.

Mortality and Morbidity

Both mortality and morbidity were high. A total of 61 operations were performed in this group of 27 patients undergoing femoro-popliteal bypasses. Sixteen patients out of 27 (60%) had more than one operation. The morbidity and mortality are summarized in Table 5. Five patients died in the immediate postoperative period (15%). The causes of death were graft infection and sepsis in one patient; false aneurysms with massive bleeding in two patients; acute myocardial infarction in two other patients. There were four instances of graft infections (13%), two of these patients expired; two patients recovered and in one of the graft had to be removed with limb survival, while in the fourth patient the infection was superficial and he recovered with the graft intact. Graft degeneration or true aneurysms of the

TABLE 4. *Heterografts in Other Locations*

No.	Patient	No. of Grafts	Clinical Course and Outcome	No. of Operations
1	G. V.	1	Ileo-femoral bypass. Patent at 24 months.	1
2	S. S.	1	Femoro-femoral bypass. Patent at 36 months.	1
3	M. P.	1	Aorto-femoral bypass. Patent at 36 months.	
4	W. A.	1	Popliteal artery replacement after aneurysm resection. Patent 36 months.	1
5	P. A.	1	Ileo-femoral closed in 3 months (young patient with severe large and small vessel disease).	1

TABLE 5. *Morbidity and Mortality*

Type	No.	
Mortality	5 (15%)	Graft infection and sepsis—1 patient False aneurysms, massive bleeding—2 patients Acute myocardial infarction—2 patients
Infection	4 (13%)	2 Patients died. 2 Patients recovered, on one the graft had to be removed with limb survival.
Graft Degeneration	2	1 Graft was ligated.
(True aneurysm)	(7%)	1 Graft replaced with second heterograft which also failed.
False Aneurysm	4 (13%)	2 Patients died from hemorrhage. 1 Graft removed, replaced with heterograft which also failed, followed by A-K amputation. 1 Graft ligated with limb survival.

heterografts occurred in two patients (7%), one graft was ligated, the second graft was replaced with another heterograft which also failed. Viability of the limb was preserved in both patients. False aneurysms formed in four patients (13%); two patients died from hemorrhage, one graft was removed and replaced with a second heterograft which also failed, and eventually an above-knee amputation was required. One graft was ligated with survival of the limb.

Heterografts for Arterio-Venous Fistulas (Table 6)

Of the four heterografts implanted in a loop fashion in the forearm, all four eventually failed. Three of them thrombosed shortly postoperatively. Thrombectomy was attempted but was unsuccessful. The fourth one developed infection following trauma over the skin overlying the subcutaneously placed graft. The infected heterograft was removed. Three of the straight forearm heterografts failed in the first three months on dialysis. All failures were due to low flow either because of advanced arteriosclerosis or because of high venous resistance due to an inadequate-size vein. None of the failures seems related to the graft itself. One patient had acute thrombosis of the graft four months following implantation during a period of hypotension. This graft was successfully declotted and has remained open now for an additional six months. Fifteen heterografts have been used for dialysis for a period of three to 14 months. Three of the 14 arm heterografts have failed, two because of infection with false aneurysm formation and one due to axillary vein phlebitis. Three of these patients also developed severe vascular insufficiency with numbness and coldness of the fingers. In two of these patients, this insufficiency progressed to gangrene of the fingers requiring amputation. In one patient the graft outflow was narrowed with a Dacron cuff, decreasing the flow from 1200 cc/min to 400 cc/min with disappearance of the vascular insufficiency symptoms.

TABLE 6. *Heterografts Used for Arterio-Venous Fistulas for Hemodialysis*
(37 Grafts in 30 Patients)

Type	No.	Failed*	Patent
Loop Foreman Grafts	4	4	—
Straight Forearm Grafts	19	4	15
Straight Arm Grafts	14	3	11

* Immediately postop or during the first two months on dialysis.

The final results are summarized in Table 7. Ten grafts failed in the first three months, giving a patency rate of 72% (this would be 81% if the four loop fistulas are excluded); one graft has failed in the 3–6 month period with a patency rate of 93% and no failures have occurred in the grafts that have been used for more than nine months. A more detailed account of the use of heterografts for A-V fistulas for dialysis will be given in a separate publication.[8]

Discussion

There is always the natural tendency both for authors to report and for journals to accept positive results. In the field of vascular prosthesis, however, knowledge of failure is just as crucial. From the paucity of clinical reports about the 3,000 grafts mentioned previously, one would have to presume that our unfortunate experience is not unique. This suspicion is reinforced by the fact that in spite of the urgent need for a satisfactory substitute for the long saphenous vein and the easy availability of the Bovine heterograft, the latter has not gained wide-spread acceptance in more than 12 years of clinical use. All patients in the first group of this report were private patients, operated upon by an experienced senior vascular surgeon (JJ) which excludes the possibility of technical factors accounting for the high incidence of failures. The high incidence of re-operation will attest to the fact that failures could not be attributed to

TABLE 7. *Heterograft A-V Fistula Followup*

Months in Use	3	6	9	12
No. of Fistulas	27	14	6	3
Patency Rate	72%*	93%	100%	100%

* This would be 81% if the four loop fistulas are excluded.

lack of aggressiveness on the part of the surgeon involved. The high morbidity, mortality, early and late failure rate encountered renders the modified Bovine heterograft an unacceptable substitute for the saphenous vein in the femoro-popliteal position.

The number of multiple operations in this group (60%) has a direct relationship to the incidence of infection, aneurysm formation, bleeding and mortality. In a contrast to this, all of the six patients with patent grafts for more than 24 months were operated only once. The small group of patients with grafts in the aorto-femoral, iliofemoral and femoro-femoral positions did well, which parallels the experience reported in the literature and is similar to that of the cloth prosthesis in these locations. The failure rate of the heterograft in the femoro-popliteal location corresponds to the experience reported by other authors using cloth grafts in that position.[5,14]

On the other hand, the modified Bovine heterograft did prove to be an acceptable substitute for the saphenous vein when used in the construction of an arteriovenous fistula for dialysis purposes. This can be concluded in spite of the relatively short follow-up because the criteria of evaluating success in these patients is different. In all these patients a standard subcutaneous arteriovenous fistula[1,7] could not be performed, therefore, the alternative was the use of a silastic cannula shunt which has a mean patency rate of six to eight months.[6] Any method which has the advantages of the arteriovenous fistula over the shunt and functions for a similar or longer period of time would be acceptable. The hemodynamic situation in this use of the heterograft is obviously entirely different. In the arterio-venous fistula one is dealing with a high-flow, low-resistance system in which a tendency to thrombosis is markedly decreased. Also, the known platelet function deficiency of the uremic patient decreases the tendency to thrombosis. True aneurysms or graft degeneration did not occur in these heterografts for the period of observation. The "loop" fistula was unsuccessful in four patients. This type of fistula has failed also when an autogenous vein has been used, and is therefore probably hemodynamically wrong.[6,8] It seems, therefore, that the modified Bovine heterograft is an acceptable substitute for the saphenous vein in the construction of an arterio-venous fistula for hemodialysis.

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A Clinical Experience with Intraoperative Autotransfusion

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Utilizing a disposable unit, intraoperative autotranfusion was employed during surgery in 53 patients admitted to the Bexar County Teaching Hospital at the University of Texas Health Science Center at San Antonio. During the two-year period of study, 26 patients underwent surgery for major traumatic injuries, 8 for ruptured ectopic pregnancy and 19 for miscellaneous emergency or elective conditions. The indication for intraoperative autotransfusion was an anticipated blood loss of 1,000 ml or more. Contraindications for its use were colon injury or localized infection. Over 325 units of blood were salvaged and returned directly to these patients during surgery. One death related to the use of the autotransfusor unit was due to massive air embolism. Twenty other deaths were associated with severe injuries and irreversible shock requiring greater than 3,600 ml of both autologous and homologous blood. Eight of these patients demonstrated severe pancoagulopathies. In the remaining patients, clotting factors and plasma or urine hemoglobin levels were transiently abnormal. However, there were no clinically apparent bleeding defects or renal problems detected. Postoperative blood cultures were consistently negative. It is concluded that intraoperative autotransfusion, when properly employed, is a safe, practical and technically feasible procedure.

SURGEONS ARE ACUTELY AWARE of the increasing problems of blood availability in the United States. Autologous blood is the ideal product for transfusion. Unfortunately, many liters of this perfectly good material are discarded during surgery each day. Much of this blood could be used safely for volume replacement. To this end, intraoperative autotransfusion is a useful concept which involves the salvage of blood lost at surgery and its immediate reinfusion. Such utilization of the patient's own blood is not new. Highmore in 1874[14] suggested that this procedure could be lifesaving after reviewing his experience with patients who died from postpartum hemorrhage. Autotransfusion was employed in 1885 by Duncan[8] of Edinburgh during extremity amputations without notable ill effects. Thies[28] in 1914 reported the use of autotransfusion in ruptured ectopic pregnancies. By 1920 there were 164 cases recorded.[5,6,10,11,13] Autotransfusion in America was first reported by Lockwood[18] who used the technique while performing a splenectomy for Banti's syndrome. Since 1924, autotransfusion has been carried out during treatment of abdominal or chest trauma and ruptured ectopic pregnancy. It has also been used during elective splenectomy, amputation and urological and neurosurgical procedures. In over 1,000 documented cases of autotransfusion the only deaths or major complications attributed directly to the procedure were associated with reinfusion of old or grossly contaminated blood.[16]

With new techniques of blood handling made available through the advent of cardiac bypass, renewed interest in intraoperative autotransfusion has developed. Recently, Symbas[26,27] has described the technique for reinfusion of blood from traumatic hemothorax in both the experimental laboratory and clinically. Klebanoff[15,16] developed a disposable autotransfusion unit in the laboratory and studied the problems of contamination and large volume autotransfusion. He reported an initial clinical trial in ten patients in Viet Nam where the device was demonstrated to be lifesaving with minimal risk.[17]

A further modification of this disposable autotransfusion unit was employed during surgery in over 50 patients admitted to the Bexar County Teaching Hospital of the University of Texas Health Science Center at San Antonio over the past two years and forms the basis of this report.

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TABLE 1. *Intraoperative Autotransfusion in 16 Patients with Penetrating Trauma Due to Gunshot (GSW) or Stab (SW) Wounds*

					Volume (ML) Blood Transfused			
Patient Name and G#	Age	Sex	Pre-op B. P.	Area of Injury	Intraop. Auto-Transfused	Homologous Blood Transfused	Total Blood Infused	Deaths
M. S. 259248	28	M	90/0	GSW pancreas, spleen, stomach & jejunum	3200	1000	4200	–
B. B. 268231	27	M	80/20	SW spleen & diaphragm	800	1000	1800	–
Y. H. 146911	19	F	120/60	SW liver & thorax	2350	3700	6050	+
F. M. 266799	28	M	60/0	GSW thoracic artery	7000	2500	9500	–
A. C. 246100	20	M	70/50	GSW jejunum & kidney	1200	2500	3700	–
J. S. 247753	34	M	80/40	GSW inf. vena cava & small bowel	6000	1500	7500	–
H. M. 248029	31	M	70/50	GSW sup. vena cava	3000	3000	6000	–
J. S. 25639	36	M	0/0	SW liver & kidney	10,000	10,500	20,500	+
G. M. 015781	21	M	109/60	SW internal mammary artery	1100	500	1600	–
R. M. 389217	27	M	80/0	GSW heart, liver, kidney & duodenum	1150	2500	3650	+
G. B. 297962	24	M	0/0	GSW aorta, liver & thorax	4700	3000	7700	+
H. L. 319208	50	M	100/60	GSW liver & stomach	600	4000	4600	–
M. R. 275824	40	M	160/40	GSW kidney, thorax & neck	4300	7500	11,800	–
T. D. 283410	27	M	102/70	GSW duodenum & inf. vena cava	1050	2500	3550	–
J. B. 282830	19	M	50/0	GSW pulmonary artery	2675	1000	3675	–
J. G. 217699	20	M	60/40	GSW porta hepatis	10,000	4000	14,000	+
	Totals			16	59,125	50,700	109,825	5

Materials and Methods

Clinical Data

The autotransfusion unit was used during operation on 52 patients admitted to the Surgical Services of the Bexar County Hospital and one patient at the Brooke Army Hospital in San Antonio from May 1971 to February 1973. The majority of these patients required an emergency operation. Intraoperative autotransfusion was employed most frequently on patients with major traumatic injuries, many of whom had suffered significant blood loss and entered the hospital in shock. Of these patients, 16 had sustained penetrating injuries (Table 1) and 10 blunt injuries to the chest or abdomen (Table 2). Other emergency patients included 8 with ruptured ectopic pregnancies (Table 3) and 10 with miscellaneous conditions (Table 4). Autotransfusion was also used in 9 elective cases (Table 5).

Clinical Protocol

The decision to use autotransfusion on a given patient was made by the resident surgeon on call after he had estimated the degree of hemorrhage and potential for further blood loss. Obvious hemorrhagic shock, a grossly bloody peritoneal lavage or culdocentesis, greater than 1500 ml of rapid blood loss from a thoracostomy tube, or

TABLE 2. *Intraoperative Autotransfusion in 10 Patients with Blunt Trauma*

					Volume (ML) Blood Transfused			
Patient Name and G#	Age	Sex	Pre-op. B. P.	Injured Organs	Intraop. Auto-Transfused	Homologous Blood Transfused	Total Blood Infused	Deaths
R. R. 273527	25	F	0/0	Liver & hepatic veins	2800	2500	5300	+
A. D. 24758	27	M	80/40	Spleen	500	1500	2000	–
A. M. 278624	24	M	100/70	Liver & tibia	1000	1000	2000	–
R. J. 281240	28	M	70/40	Spleen & subdural	200	1500	1700	–
E. R. 247243	19	M	150/100	Ileum	600	0	600	–
E. M. 040621	14	M	100/58	Spleen & kidney	900	0	900	–
H. R. 277597	24	M	60/0	Liver & hepatic veins	1100	3500	4600	+
R. C. 305499	22	M	0/0	Hepatic & portal veins liver & spleen	4500	4000	8500	+
R. F. 311895	30	M	40/0	Liver & hepatic veins	3000	3000	6000	+
G. G. 281472	25	M	130/80	Pancreas & spleen	2000	3000	5000	–
	Totals			10	16,600	20,000	36,600	4

TABLE 3. *Intraoperative Autotransfusion in 8 Patients with Ruptured Ectopic Pregnancy*

Patient Name & G#	Age	Preop. B. P.	Volume (ML) Blood Transfused Intra-op Auto-Transfused	 Homologous Blood Transfused	 Total Blood Infused	Deaths
V. C. 261459	20	—	500	0	500	—
R. B. 249992	22	110/70	1500	0	1500	—
M. R. 246670	41	140/90	1100	0	1100	—
R. M. 279965	33	100/80	900	1500	2400	—
H. C 281963	31	130/90	1100	1500	2600	—
O. M. 152252	22	98/70	1400	1000	2400	—
H. M. 319766	30	80/40	1450	500	1950	—
T. V. 249316	19	—	2500	0	2500	—
Totals		8	10,450	4,500	14,950	0

an anticipated operative blood loss of 1000 ml or more were all sufficient indications for having the autotransfusion unit readied for use. During operation, attempt was made to retrieve any quantity of blood regardless of the amount. Autotransfusion was employed in patients with associated wounds of the stomach or small intestine when blood losses from solid organ or vascular injury were relatively large. The presence of purulent infection or colon injury precluded the use of intraoperative autotransfusion. The contraindications are still being identified, but where blood losses are excessive, even these sources of contamination may become insignificant. Blood cultures taken immediately postoperative have been consistently negative in our cases.

For elective surgery the autotransfusion unit was placed on standby for selected major procedures if large blood losses were anticipated, or blood was difficult to obtain because of the patient's rare blood type, and for urgent operations when bleeding or clotting difficulties were anticipated. Where possible, coagulation studies, plasma and urine hemoglobin determinations, and blood cultures were carried out preoperatively and periodically postoperatively for several days.

Design and Operation of the Autotransfusor Unit

The autotransfusor unit consists of a plastic Bentley[*] cardiotomy reservoir modified for aspiration, filtration, and delivery of blood (Fig. 1). A vacuum is created by a single unit rollerhead pump which allows aspiration from the operative field to a 1500 ml capacity reservoir. The blood is filtered, defoamed, and finally reinfused by regulating the pressure within the reservoir at the air-liquid interface. The pore size of the Bentley filter is 125 μ and therefore allows the passage of formed blood elements

TABLE 4. *Intraoperative Autotransfusion in 10 Patients Requiring Emergency Surgery (Miscellaneous Group)*

Patient Name and G#	Age	Sex	Pre-op B. P.	Diagnosis	Volume (ML) Blood Transfused Tntraop. Auto-Transfused	 Homologous Blood Transfused	 Total Blood Infused	Deaths
A. M. 277638	40	M	60/40	Bleeding gastritis & cirrhosis	1650	5500	7150	+
F. W. 261501	58	F	90/60	Perforation ventricle by cardiac cath.	970	3500	4470	—
A. S. 249997	71	M	70/0	Bleeding liver abscess cavity	8700	1500	10,200	+
B. B. 227610	35	F	60/0	Ruptured vessels of renal transplant	18,000	9000	27,000	+
E. G. 255386	30	F	110/90	Needle lacration of liver with hepatitis	3400	1000	4400	+
B. V. 102489	82	M	80/40	Ruptured abdominal aneurysm	3750	4500	8250	+
V. O. 315480	64	M	140/80	Ruptured abdominal aneurysm	500	3000	3500	—
M. G. 139352	70	M	160/100	Bleeding hepatoma	4700	3000	7700	+
B. R. 327350	53	M	70/40	Ruptured abdominal aneurysm	5000	7000	12,000	+
M. V. 125647	57	F	—	Right hepatectomy Ca of gallbladder	6100	0	6100	+
Totals				10	52,770	38,000	90,770	8

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[*] Autotransfusion Unit, Bentley Laboratories, Inc., Santa Ana, California.

TABLE 5. *Intraoperative Autotransfusion in 9 Patients During Elective Surgery*

					Volume (ML) Blood Transfused			
Patient Name and G#	Age	Sex	Pre-op B. P.	Procedure & Diagnosis	Intra-op Auto-Transfused	Homologous Blood Transfused	Total Blood Infused	Deaths
G. S. 033555	49	F	110/80	Bleeding laminectomy T. B. of spine	1200	10,500	11,700	+
I. R. 045947	53	F	130/70	Cirrhosis, hypersplenism, cholecystitis, pancreatitis	8500	6000	14,500	+
L. L.—Brooke Army	49	M	120/70	Shunt for cirrhosis & portal hypertension	10,000	6000	16,000	+
P. M. 074408	59	M	134/74	Shunt for cirrhosis & portal hypertension	2400	5000	7400	+
A. B. 242451	8	M	110/70	Right hepatectomy Wilm's tumor	1000	0	1000	—
A. G. 202380	57	M	140/88	Abdominoperineal carcinoma, rectum	150	1000	1150	—
H, S. 287780	58	F	100/60	Splenectomy Felty's syndrome	950	1000	1950	—
B. L. 296844	69	M	110/80	Nephrectomy pyelonephritis	500	0	500	—
V. J. 234915	59	F	180/100	Shunt for cirrhosis & portal hypertension	600	0	600	—
Totals				9	25,300	29,500	54,800	4

while trapping clots, bits of tissue, or other particulate matter which may be larger than 125 μ.

The autotransfusor device is entirely prepackaged and sterile. It is opened on the operating table. The suction tip and appropriate length of tubing are retained by the surgical team. The remaining inflow tubing and unit are passed off to a technician who hangs up the reservoir and inserts the inflow tubing into the head of the roller pump. The unit is then primed with 200–300 ml of electrolyte containing solution with 3000 units of heparin per liter. When all air in the lines is removed, the outflow tubing may be safely connected to the patient through two large bore intravenous catheters (e.g. 14 gauge or larger) usually inserted in the upper extremities. Blood is aspirated from the abdominal or thoracic cavities and collected in the reservoir. By controlling the air pressure in the reservoir, blood may be returned rapidly and continuously at a maximum flow of 600 ml/min or reinfused slowly and intermittently depending on the needs of the situation. Between collections of blood the inflow tubing is rinsed occasionally by aspirating the heparinized priming solution. In this series, the patients were not given additional heparin at the operating table.

Results

The total blood salvaged during the period of study was 164,245 ml which represents more than half of the 306,945 ml of total blood transfused (Table 6). Volumes autotransfused ranged from 150 ml to 18,000 ml. The average salvaged blood per patient was approximately 3000 ml.

Of the 53 patients undergoing autotransfusion, there were 21 deaths (40%). One was related to the use of the autotransfusor unit. This patient emphasizes the hazard of air embolism. Death was due to massive air infusion which occurred during autotransfusion for an elective spleno-renal shunt. Blood was allowed to run out of the reservoir and air was pumped into the intravenous lines.

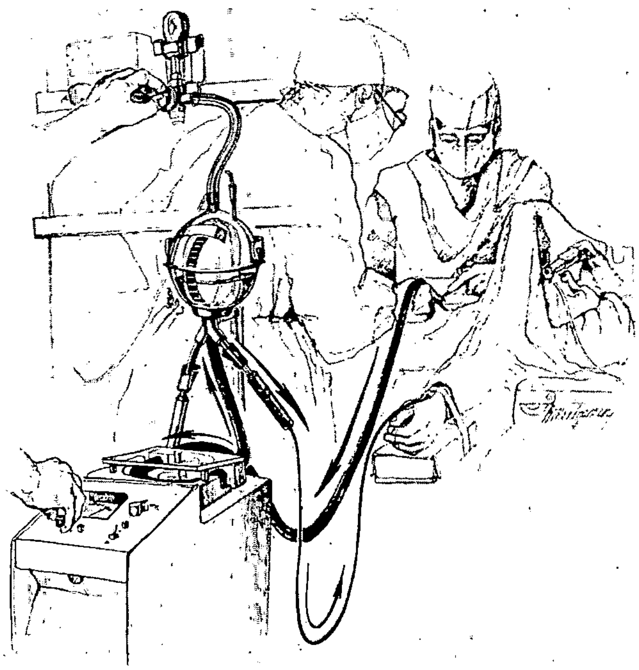

FIG. 1. The autotransfusor unit is seen in operation during surgery. Blood is aspirated from the operative field by the surgeon. The rate of aspiration is controlled by the technician by adjusting the rollerhead pump speed. Blood is filtered and collected in the reservoir. Delivery of blood to the patient via the onflow tubing is controlled separately by varying the air pressure built up in the reservoir by the pump. Thus intravenous administration may be stopped while blood is being collected and visa versa.

TABLE 6. *Grand Totals: Intraoperative Autotransfusion Volume (ML) Blood Transfused*

No. Cases	Intraop. Autotransfusion	Homologous Transfusion	Total Transfused	Deaths
53	164,245	142,700	306,945	21 (40%)

At the present time, a trained technician must operate the device as his sole responsibility and never allow the lines to the patient to be open when the reservoir blood level is below 200 ml.

Other deaths were due to major vascular or hepatic injuries which were uncontrollable or irreparable in spite of massive blood replacement. Many of these patients were in profound shock preoperatively (Tables 1 & 2). There were no deaths among the women who underwent intraoperative autotransfusion during surgery for ectopic pregnancy (Table 3). The very high mortality in the miscellaneous emergency group was commensurate with the severity of the lesion as well as the magnitude of blood replacement (Table 4). Associated diseases such as cirrhosis as well as the total blood transfused contributed to mortality among the elective patients (Table 5).

Analysis of the effects of intraoperative autologous blood on mortality and coagulation factors is difficult because of the frequent associated homologous blood transfusions. Nevertheless, the data were arbitrarily divided with respect to volumes transfused. Groups analyzed included patients who received greater or less than 1500 ml of autotransfused or homologous blood and those receiving a total volume of greater or less than 3600 ml (Table 7).

Mortality was significantly higher in patients transfused with over 1500 ml of either autotransfused or homologous blood. There were no deaths among the 22 patients transfused with a total volume of less than 3600 ml. However, there were 14 deaths among the 17 patients receiving total volumes of blood greater than 7000 ml (82% mortality). In the intermediate group of 14 patients there were 7 deaths (50% mortality).

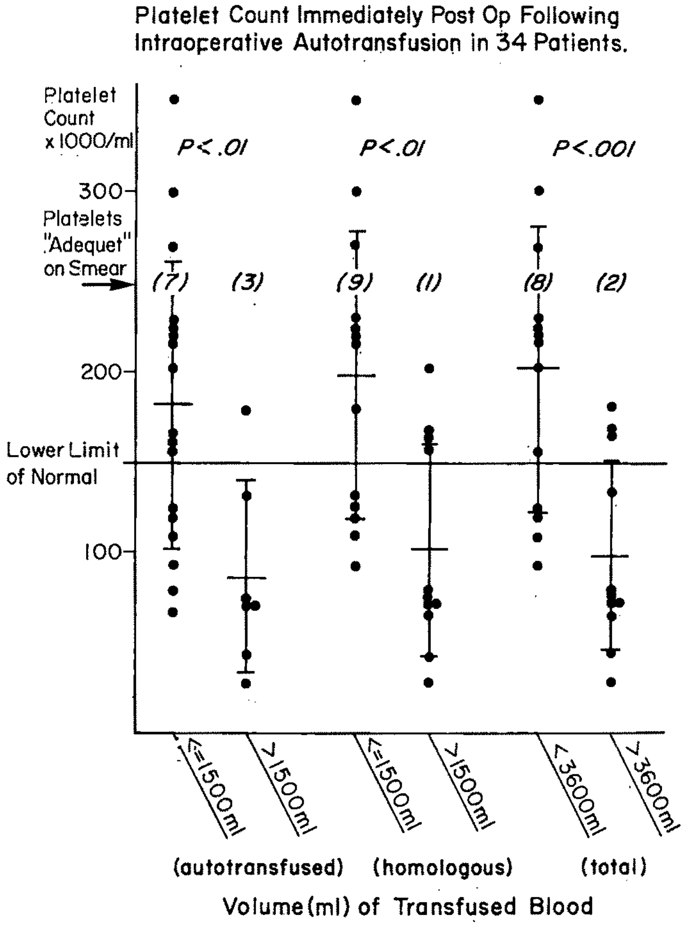

FIG. 2. Platelet determinations are divided into high and low volume groups of autologous, homologous, or total blood transfused. The dots represent individual patients and each vertical line with cross bars indicates the mean and standard deviation. P values were determined by the *t test*. The numbers in parentheses represent additional patients whose blood smears were analyzed for platelets.

Eight patients in the high-volume group demonstrated severe multiple clotting deficiencies with persistent bleeding from raw surfaces and puncture sites. Further detailed review of these difficult coagulation problems revealed that three of these patients had serious coagulation defects preoperatively. There were two survivors following surgery for severe trauma whose pan-coagulopathies responded to vigorous administration of fresh whole blood, fresh frozen plasma and epsilon amino carpoic acid. Two patients in this group died of massive injuries with profound shock and uncontrollable hemorrhage.

TABLE 7. *53 Patients Analyzed as to Mortality and Coagulopathies in Three Volume Categories of Blood Transfused*

	Autotransfused		Homologous		Total		
	< = 1500 ml	> 1500 ml	< = 1500 ml	> 1500 ml	< 3600 ml	> 3600 ml	
						< 7000 ml	> 7000 ml
Patients	27	26	26	27	22	14	17
Coagulopathies	0	8	1	7	0	0	8
Deaths	3	18	3	18	0	7	14
%	11%	70%	12%	67%	0%	50%	82%

The remaining patient was a cirrhotic 82-year-old man who died of a myocardial infarction one day post surgical repair of a ruptured aortic aneurysm. His coagulation studies were improving at the time of death.

Usually immediately following the larger volume autologous, homologous, and/or total blood transfusion, platelets, prothrombin time (PT) and partial thromboplastin time (PTT) were significantly affected but rapidly returned to normal in the postoperative period unless, as previously noted, the total volume transfused was very high. Clotting factors were only minimally affected following smaller volume transfusions even through significant fibrin and platelet clots were collected on the filters. An estimation of platelets was made immediately postoperative in 34 patients who had no known preoperative coagulation defects (Fig. 2). Platelet counts were carried out in 24 of these patients. The mean platelet level was within the normal range in patients receiving 1500 ml or less of autotransfused or homologous blood and less than 3600 ml of total blood transfused. However, the group of patients receiving greater than 1500 ml of autotransfused or homologous blood and greater than 3600 ml of total volume transfused had a significantly lower mean platelet level which was below normal. Prothrombin times were done in 27 patients and partial thromboplastin times in 25 patients immediately postoperative (Figs. 3 and 4). The mean values of these factors were within normal limits in the groups of patients transfused with the lower volumes of blood in all three categories. Mean values of prothrombin time and partial thromboplastin time were significantly abnormal in the groups of patients who received the higher volumes of autologous or homologous blood.

Evidence for clinically significant blood destruction during intraoperative autotransfusion was lacking. The highest recorded elevation of plasma free hemoglobin was 250 mg%. Though mild to moderate hemoglobinuria occurred in many patients, there was no case of postoperative renal failure. Plasma hemoglobin levels were determined in 25 patients (Fig. 5). Immediately postoperative mean values were higher in all three high volume categories but comparison with the low volume groups revealed significant differences only in the total and homologous transfusion categories. Urine was tested for the presence of hemoglobin in 36 patients following surgery (Fig. 6). The presence of hemoglobinuria in these patients tested was significantly higher in all of the high volume categories.

Discussion

Intraoperative autotransfusion offers the surgeon and patient many advantages. The autotransfusor unit can be used in any surgical procedure where there is significant blood loss, including elective orthopaedic[12] and vascular

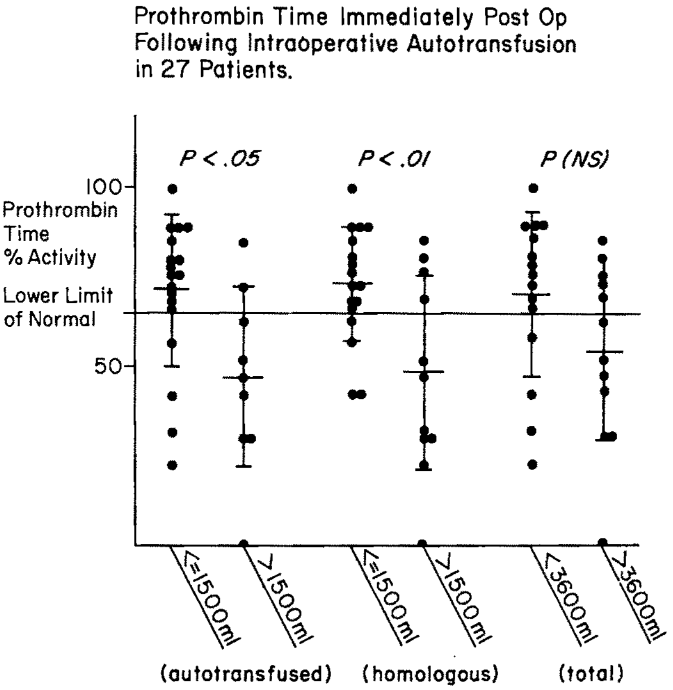

FIG. 3. The Prothrombin Time of each patient was converted to Prothrombin Time % Activity using a standard citrate activity curve. Patients are divided into high and low volume groups of autologous, homologous, or total blood transfused. The dots represent individual patients and each vertical line with cross bars indicates the mean and standard deviation. *P* values were determined by the *t test.*

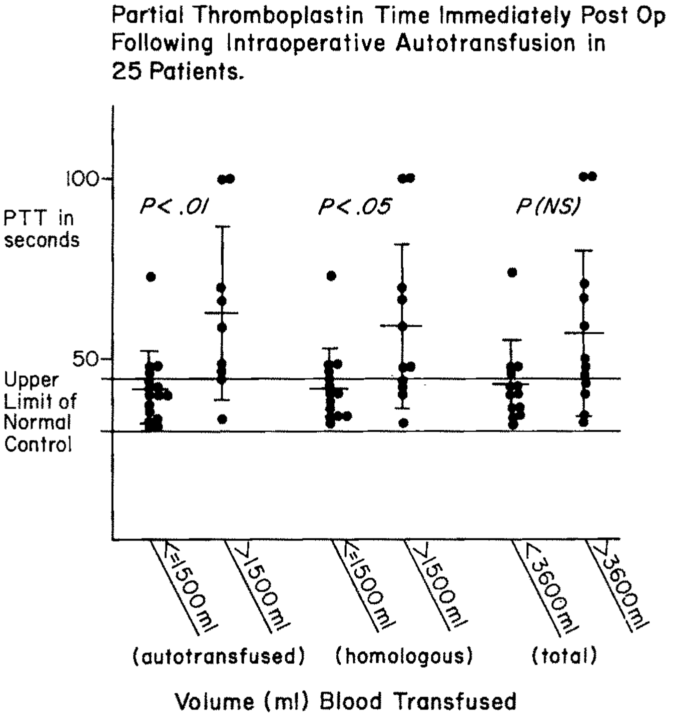

FIG. 4. Partial Thromboplastin Time determinations are divided into high and low volume groups of autologous, homologous, and total blood transfused. The dots represent individual patients, and each vertical line with cross bars indicates the mean and standard deviation. *P* values were determined by the *t test.*

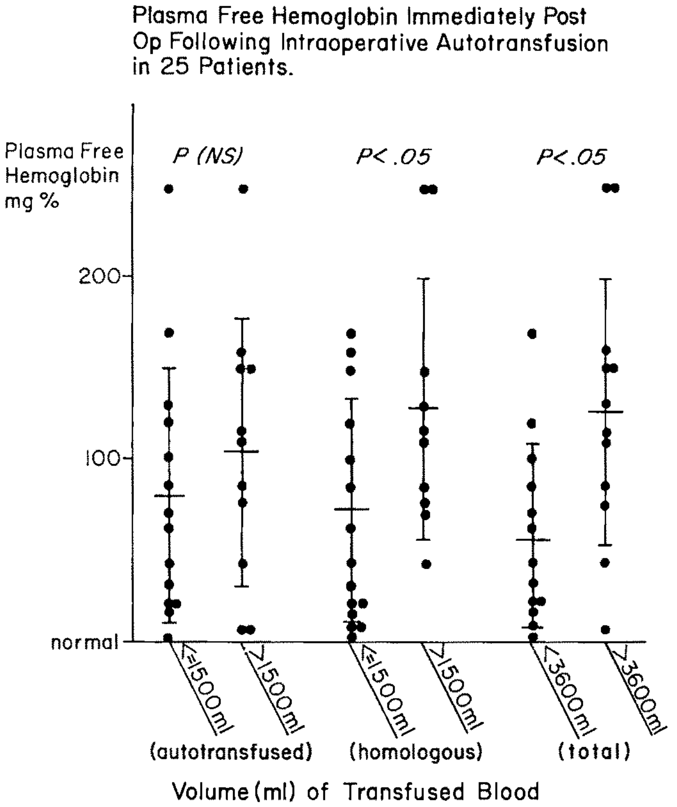

FIG. 5. Plasma Free Hemoglobin levels are divided into high and low volume groups of autologous, homologous, and total blood transfused. The dots represent individual patients, and each vertical line with cross bars indicates the mean and standard deviation. *P* values were determined by the *t test.*

surgical procedures.[3,4] In its present form the unit is relatively simple and thus requires minimal training to operate. Within minutes the autotransfusor unit can be set up for rapid reinfusion of large volumes of blood even before blood can be obtained from the blood bank. In two of our cases, death from exanguinating hemorrhage was averted when over 3000 ml of blood was autotransfused prior to receiving the first banked unit. We have calculated that the cost of both the autotransfusor unit and technician time is about that of 2 units of blood. Therefore, with blood losses of 2 units or more intraoperative autotransfusion becomes economically advantageous. Even more important, the risks of homologous serum hepatitis or other donor blood-borne diseases are avoided. Obviously, blood which is autotransfused at surgery does not cause hemolytic transfusion reactions or sensitizations to foreign red cells, platelets, or leukocytes.

Other investigators having clinical experience with autotransfusion in trauma surgery have reported survivors following autotransfusion of large volumes.[7,20] Rakower[20] utilized full heparinization in his patients, reported few pancoagulopathies, but did note prolonged hemostatic difficulties intraoperatively. The explanation for coagulation defects following massive autotransfusion is not entirely clear. Certainly, the deposition of fibrin clots on the filters of the reservoirs with entrapment of platelets must play a role since circulating platelets diminish rapidly during autotransfusion. We noted a similar accumulation of fibrin clots in the filters and drop in platelets in our patients especially following high volumes of blood replacement. Likewise, labile factors V and VIII which are absent in banked blood have also been observed to diminish following massive hemorrhagic shock.[25] During intraoperative autotransfusion a progressive decrease in blood levels of factors V and

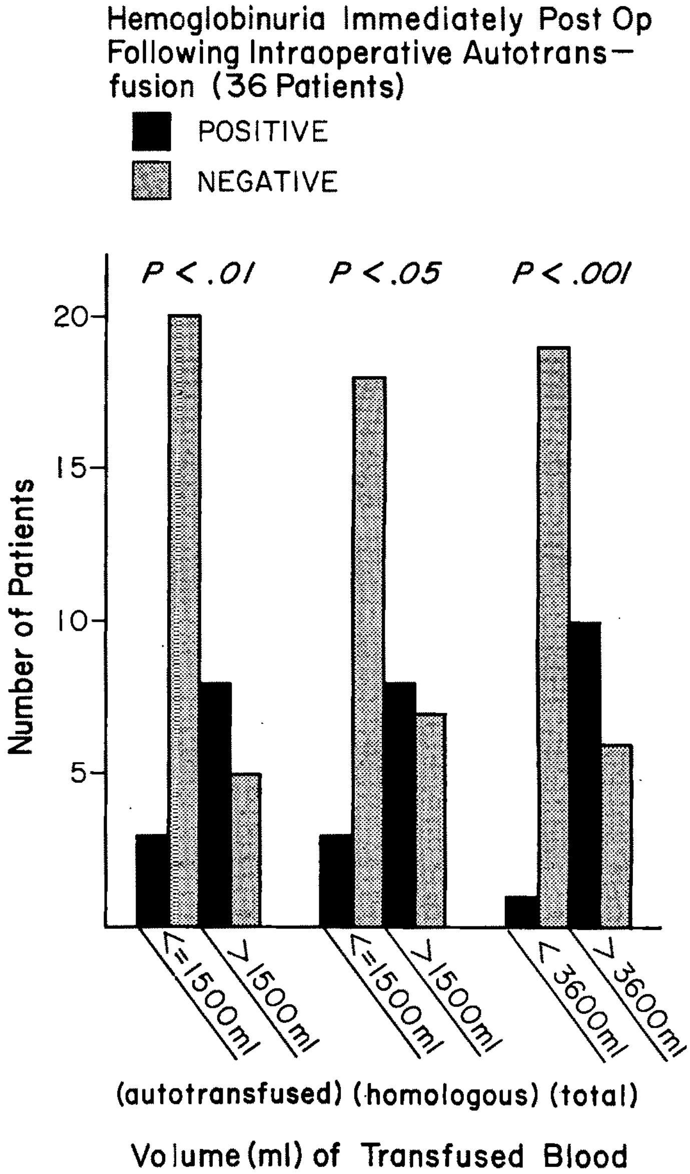

FIG. 6. Patients with and without hemoglobinuria are divided into high and low volume groups of autologous, homologous, and total blood transfused. *P* values were determined by the chi-square test.

VIII have been observed as the deposits of fibrin clot on the filters increase.[9,17,23] Significantly abnormal levels of prothrombin time and partial thromboplastin time were seen in our patients following higher volume transfusions. Autotransfusion of more than 6 liters in our patients often implied massive trauma to multiple organ systems. The effects of prolonged severe shock with associated hypoxia and acidosis especially with hepatic and renal injury also predisposed the patient to the development of coagulation defects.

Additional potential complications of autotransfusion include air embolism, infection and blood destruction. As mentioned, air embolism is a preventable complication through the utilization of a trained operating room technician whose sole responsibility is running the unit. Infection has not been noted in any of our patients as a direct result of autotransfusion, and all postoperative blood cultures have been sterile. This is the same experience reported by others.[16] Dowling[7] reported six patients operated upon for major traumatic injuries which included colon penetration in which intraoperative autotransfusion was carried out without postoperative sepsis. Indeed, where the volumes of autotransfused blood are large, such contamination becomes insignificant. When the use of autotransfusion is a lifesaving measure, the presence of contamination should not automatically preclude the use of this system. Where there is a serious question about the usability of salvaged blood, the aspirated blood may be collected in standard blood storage bags until a proper assessment has been made.

Anticoagulation techniques have varied during autotransfusion in different centers.[3,7,12,20,26,27] Blood destruction and coagulation can be prevented by partial heparinization through the use of a heparin containing priming solution which is the technique employed in our series. Others[20] have suggested complete systemic heparinization or ACD anticoagulation especially where blood losses are greater than 3 liters. When large volumes of autotransfusion are required, use of platelets and fresh frozen plasma becomes necessary to avoid coagulopathies. We administer one unit of fresh frozen plasma for every 3 units of blood autotransfused. Platelet infusions are seldom required unless more than 6 liters of blood have been lost.

Some investigators have varied the pore size of filters used during autotransfusion and feel that smaller 40 μ filters prevent microemboli to the lungs.[7] The filtration of the autotransfused blood through 125 μ filters is adequate for the designed purpose of removing particulate contamination. Except for one case of severe chest trauma there was no evidence of diffuse lung problems postoperative in any of our surviving patients who received autotransfused blood. It is likely that banked blood plays a role in lung damage through microemboli.[19,21,24] Therefore, some have suggested that banked blood be administered through a 40 μ filter.[2,22–24] Apparently, fresh autotransfused blood does not form microaggregates unless it is stored prior to transfusion.[24]

With the current demands on hospital blood banks, it has become apparent that blood must be conserved carefully as one of our national resources. As part of a thoughtful blood conservation program the operative requirements for blood can be significantly reduced by instituting intraoperative blood salvage programs. In addition, the high risk of hepatitis following massive transfusions can be avoided by use of valuable autologous blood hitherto discarded into the wall suction. Although many important aspects of this procedure require further investigation we have found that intraoperative autotransfusion is a safe, practical and feasible technique.

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Metastatic Carcinoid to the Liver Treated by Hepatic Dearterialization

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A historical review of work bearing on the rationale for hepatic artery ligation in the treatment of malignant disease in the liver is presented, particularly the early work showing that malignant disease of the liver is supplied primarily by the arterial circulation and not by the portal. A review is presented of some clinical reports dealing with the effectiveness of this approach and our own limited experience with three cases presented briefly. The major emphasis is placed on the metabolic, arteriographic, microscopic and clinical studies on one patient with the carcinoid syndrome who was followed carefully over several years, treated initially by hepatic resection, later by chemotherapy and finally by hepatic dearterialization as the tumor re-grew and the carcinoid syndrome again became incapacitating. Clinical remissions was documented by changes in the excretion of 5-hydroxy-indole-acetic acid and by comparison between pre- and post-op arteriography and by microscopic sections taken at re-exploration for drainage of a necrotic area in the liver.

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BECAUSE of the recent surge of interest in the use of hepatic artery ligation as a method of control of primary and secondary cancer of the liver, we are reporting a case of symptomatic metastatic carcinoid tumor in the liver in which striking subjective and objective improvement was achieved in this way. In two other cases (metastatic adenocarcinoma and melanoma), no obvious effects were noted but the near terminal stage of the disease made evaluation difficult.

Madding and Kennedy[9] have recently published an extensive review of the circulation of the liver relative to the effects and therapeutic uses of hepatic artery ligation. Markowitz[11] first suggested that hepatic artery ligation might be useful in the palliation of metastatic cancer to the liver and in 1954, Breedis and Young[6] demonstrated that malignant tumors in the liver derived their blood supply almost exclusively from the hepatic artery. It was not until 1966, however, that definite effects of dearterialization on cancer both in man[14] and in laboratory animals[15] was shown by Nilsson. During the past two years, further reports have appeared. Interestingly, in three,[3,10,13] carcinoid metastases, as in our experience, seemed the most favorable tumor. Because of the number of advanced cancer and cachectic patients, the operative mortality was high, ranging from 10 to 40%. Overall results are also difficult to evaluate because of the small series and the variety of cases. Almersjo and colleagues[2] reported on 17 of 27 patients who survived the immediate postoperative period and concluded, as did Gulesserian, Lawton and Condon,[7] that, while there was clear evidence that dearterialization leads to necrosis of the majority of tumor cells, the procedure should be combined with chemotherapy for long-term palliation. The collateral blood supply to the liver is extensive[12] and demonstrable restoration of blood flow early in the postoperative course[5,8] may account for some of the failures. Plengvanit *et al.*[16] showed in postoperative angiographic studies on 20 patients that varying amounts of collateral arterial blood supply developed most commonly through the inferior phrenic and subcostal vessels. The location, extent and technique of the ligation may be of considerable importance in achieving adequate dearterialization as will be discussed later.

The case which we describe here in detail documents clearly the effect of hepatic dearterialization on the carcinoid syndrome, with pre- and postoperative angiography, biochemical parameters and histopathology.

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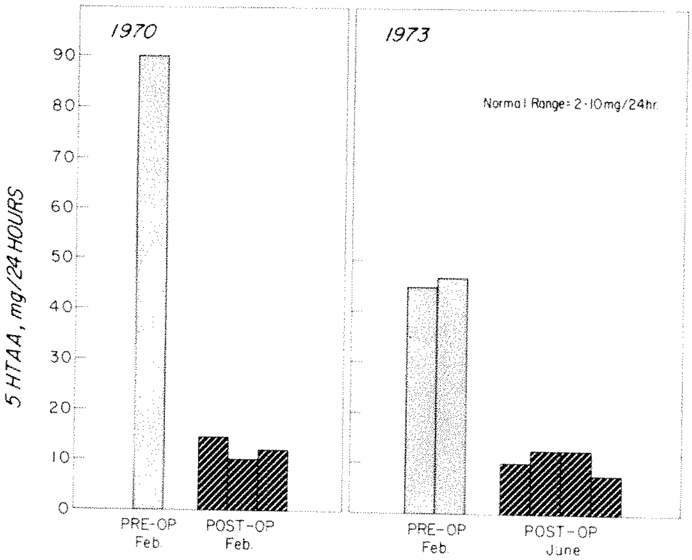


FIG. 1. Levels of 5-hydroxy-indole-acetic acid in the urine on two admissions for partial resection and later for dearterialization.

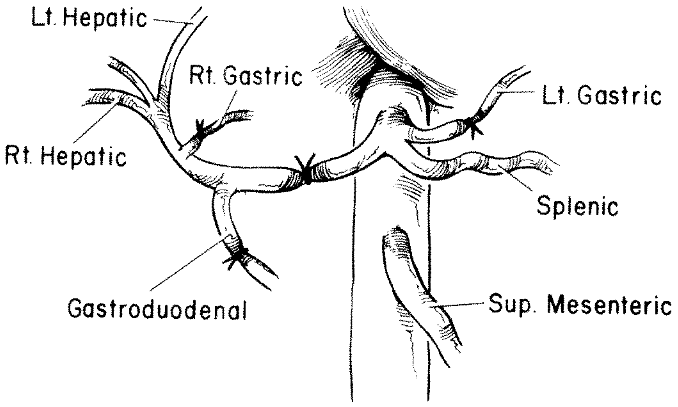


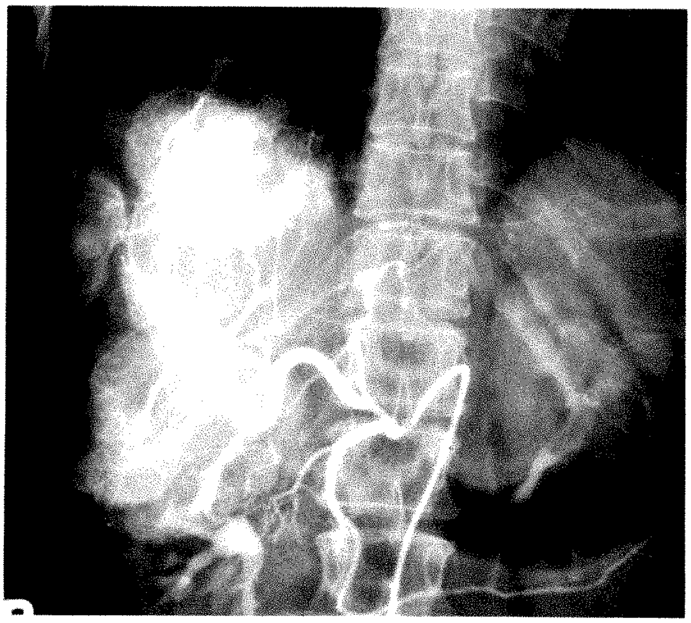
FIG. 2. Anatomical location of arterial interruptions.

Case Report

M.C., a 53-year-old married female was admitted to the New England Deaconess Hospital for the fourth time in April, 1973 with recurrent and progressive carcinoid syndrome. The patient's symptoms dated back to 1966, but were not documented medically until her first admission in February of 1970 at which time a resection of a primary tumor of the ileum and a partial hepatic resection were carried out. Although metastatic tumor remained in the residual liver, considerable symptomatic relief was accomplished. Slowly progressive recurrence became apparent, however, and was documented biochemically on a subsequent admission (Fig. 1). By 1973, she had become increasingly incapacitated and on May 7, 1973, dearterialization was carried out as shown in Fig. 2. A preoperative celiac arteriogram (Fig. 3a) showed the extent of the highly vascular tumor nodules in the liver. Postoperatively, a transient period of derangement in liver function tests (Fig. 4) occurred but most significantly, there was a striking decrease in the excretion of 5-HIAA (Fig. 1) and a nearly complete absence of arterial inflow by angiography (Fig. 3b); the only visualized artery five weeks after surgery was a small branch of the inferior phrenic.

Because of persistent low grade fever and drainage, re-exploration was carried out six weeks after the initial operation. The large tumor masses shown by angiography (Fig. 3a) had become completely necrotic and thick purulent liquid material and semisolid debris were evacuated. Microscopic examination was interesting; the large necrotic areas showed "ghost" cells consistent with carcinoid origin, some very small tumor nodules appeared viable both grossly and microscopically and the intervening liver parenchyma was normal except for a few foci of degeneration and fibrosis.

Following the second operation, the patient did well and was



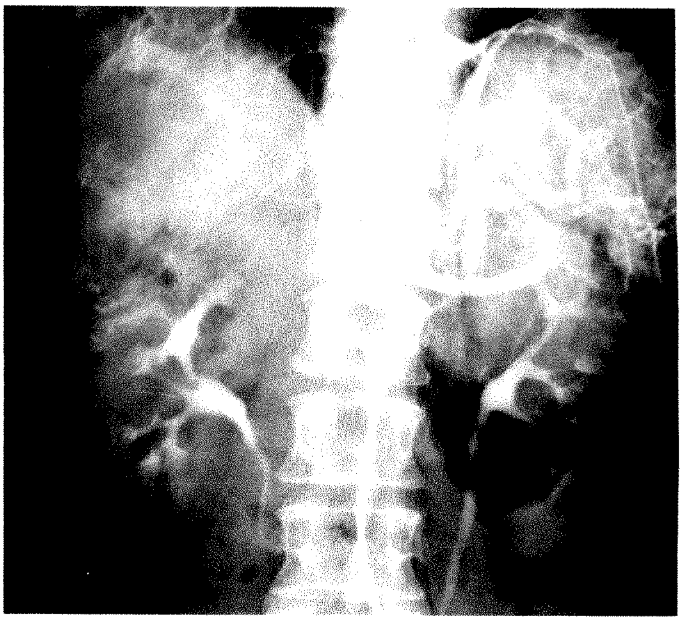


FIG. 3a. (Left) Preoperative celiac arteriogram showing multiple tumor nodules. FIG. 3b. (Right) Postoperative celiac arteriogram following hepatic artery ligation. One remaining collateral vessel can be seen.

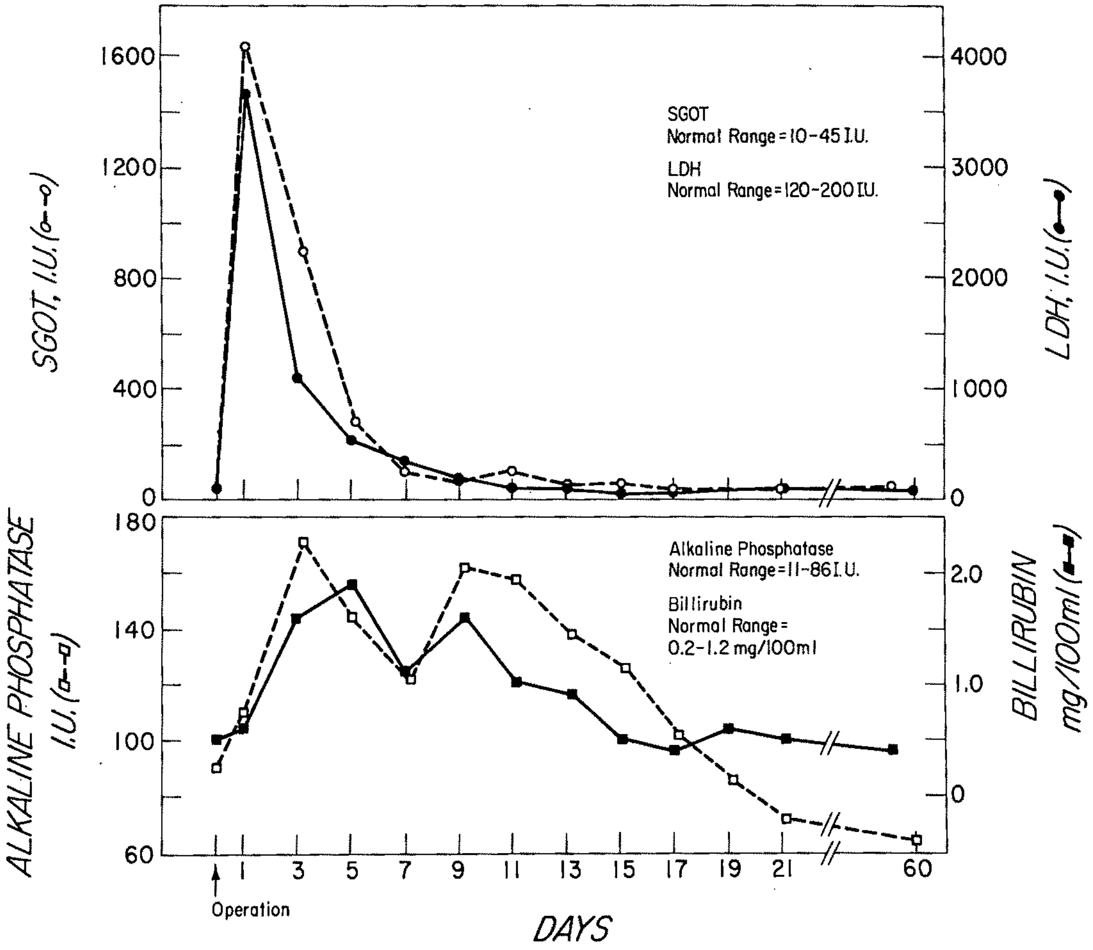


FIG. 4. Selected liver function tests following hepatic dearterialization.

discharged in June, 1973. At the time of submission of this report (November, 1973), she has minimal symptoms of occasional flushing and has resumed a normal life.

Discussion

On the basis of the limited clinical experience available to date in the literature, it is difficult to evaluate the role of hepatic dearterialization in the treatment of unresectable malignant disease of the liver. On the basis of one of our own cases and five others in three separate reports,[3,10,13] arterial ligation would appear to be an effective method of control of the distressing symptoms of carcinoid tumor in the liver; presumably similar effect might be achieved in other slow growing endocrine tumors such as insulinoma. In other metastatic malignancy, (breast, gastrointestinal, melanoma, etc.), randomized studies in carefully selected patients with and without adjunctive chemotherapy seem indicated since the reports available do not warrant full support or complete exclusion of hepatic dearterialization as a form of treatment. Primary liver cell carcinoma is relatively common in parts of Africa and Asia and Balasegaram[4] has reported in 24 patients treated in Malaysia by complete hepatic dearterialization; he concluded that this procedure had a definite place in palliative treatment of these tumors provided that patients with severe liver impairment or a significant degree of cirrhosis were excluded.

Reference has been made to the extensive collateral circulation available to the liver after hepatic artery ligation[1,12] and rapid development of arterial inflow has been demonstrated.[5,8,16] For this reason, the technique of ligation is undoubtedly important; proximal ligation of the main hepatic artery should be combined with distal ligation of possible collateral pathways as shown in Fig. 2, and division of the falciform, coronary and triangular ligaments as well as any obvious branches of the inferior phrenic artery. For adequate evaluation of case reports in the future, the completeness of the dearterialization should be described and defined whenever possible by post-operative angiography.

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Atypical Proximal Coarctation of the Aorta:

Reconstruction by Means of a Heparin-Coated Temporary Shunt Bypass

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Coarctation of the aorta may be found proximal to or involving the left subclavian artery. In this situation, adequate collateral may not be present, making aortic occlusion unduly dangerous. Simple and effective bypass protection can be achieved with a heparin-coated temporary shunt as illustrated in two patients described in this report.

COARCTATION OF THE AORTA usually occurs just distal to the origin of the left subclavian artery, but may involve or be proximal to this vessel.[3] The unusual proximal coarctation is identified by unilateral hypertension in the right arm, a diminished left radial pulse, and the absence of left-sided collateral circulation. These anatomic and pathologic alterations materially affect the difficulty of the operative procedure. Collateral circulation may not be adequate to protect the spinal cord, or to decompress the proximal compartment during aortic occlusion.[1] This report describes the use of a heparin-coated temporary shunt bypass in the management of two patients with coarctation proximal to or involving the left subclavian artery.

The safety and advantages of a heparin-coated temporary shunt have been clearly demonstrated in the resection of aneurysms of the descending thoracic aorta[12,14] and in reconstruction of the innominate artery.[13] Development of a non-thrombogenic surface by wall-bonded heparin was pioneered and accomplished by Gott[15] using brittle graphite-coated surfaces exposed to benzalkonium chloride and to heparin. Recently, heparin coating of flexible polymers by a simple solvent immersion technique has become possible.[9] The heparin-coated shunt used in these cases was designed by Gott[7] (Fig. 1). The catheter is transparent, flexible, and can be clamped without danger to the thrombo-resistant surface. The technique does not require an accessory pump or total body anticoagulation and, therefore, considerably simplifies the operation and reduces the hazard of the bypass procedure.

Case Reports

Case 1. A 20-year-old black male was noted to have a heart murmur at age four. He was subsequently lost to follow-up, remaining well until November, 1971. At that time, he began to notice exercise intolerance and morning headaches. Symptoms persisted and one year later, a pre-employment physical exam revealed severe hypertension in the right arm with diminished left upper and lower extremity pulses.

On March, 1973, he was referred to North Carolina Memorial Hospital for further evaluation. Blood pressure was 185/110 mm Hg in the right arm, and 132/114 mm Hg in the left arm. The left radial pulse was clearly diminished. The systolic pressure in both lower extremities was 120 mm Hg by palpation. A loud systolic murmur was audible over the entire precordium and posterior chest, but heard best in the left anterior, superior chest. Voltage criteria for left ventricular hypertrophy was present on the electrocardiogram. Chest x-ray suggested left ventricular enlargement with a prominent ascending aorta.

Cardiac catheterization was performed on March 22, 1973, documenting the marked central aortic hypertension with normal left ventricular function. Angiography demonstrated coarctation of the thoracic aorta proximal to the origin of the left subclavian artery (Fig. 2). One month later, a left lateral thoracotomy incision exposed the coarctation proximal to the take-off of the left subclavian artery. The obliterated ligamentum arteriosus was proximal to the origin of the left subclavian artery. A small anomalous vessel, presumably the left vertebral artery, arose from the post-stenotic aorta adjacent to the subclavian vessel. An attempt to cross-clamp the aorta resulted in extreme proximal hypertension (300+/233 mm Hg) with collapse of the distal aorta, and bradycardia. A heparin-coated shunt bypass was then placed from the ascending aorta to the left external iliac artery. The shunt allowed occlusion of the aorta without increase in proximal pressure. Distal perfusion appeared adequate with maintenance of urinary output. Excision of the coarctation with end-to-end anastomosis was accomplished (Fig. 3).

On the evening of operation, the patient experienced paradoxical

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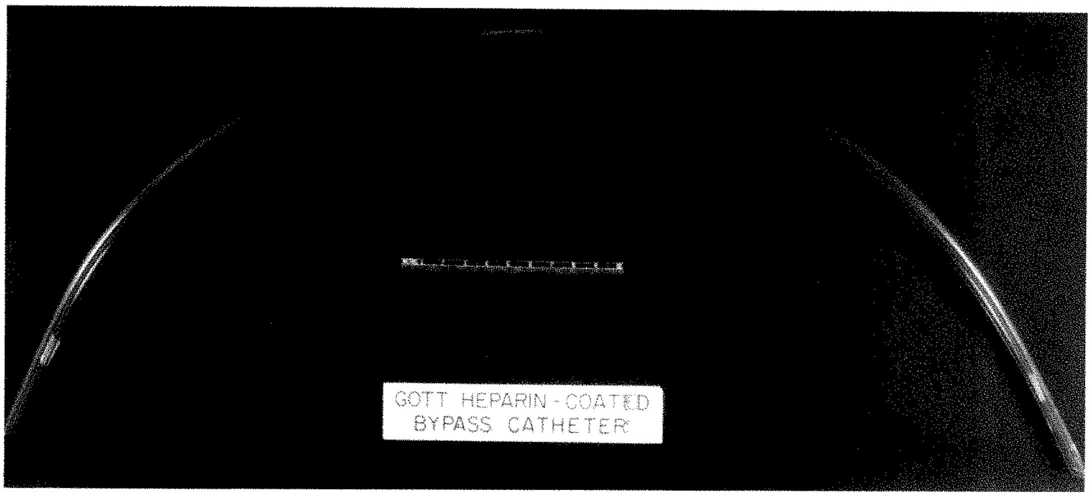

FIG. 1. A unitized polyvinyl heparin-coated catheter which is transparent, flexible and can be clamped without injury to the thrombo-resistant surface.

hypertension which responded to propanalol and hydrazaline. The recovery period was further complicated by transient lobar atelectasis. His convalescence was rapid and he has returned to work. He is normotensive on medication (130/80 mm Hg), all pulses are full, and he is free of symptoms.

Case 2. A 15-year-old white male was admitted to North Carolina Memorial Hospital on June 11, 1973 with a three-year history of leg pains on exertion. A murmur had been noted in infancy and diagnosed as coarctation of the aorta. Admission physical examination revealed a blood pressure of 150/75 mm Hg in the right arm and 130/70 mm Hg in the left arm. There was a grade IV/VI systolic murmur heard best at the upper left sternal border. The femoral pulses were palpable, but diminished with a definite pulse lag between radial and femoral pulses. The chest x-ray revealed no abnormality and the electrocardiogram demonstrated only left axis deviation. Angiography demonstrated coarctation of the aorta involving the origin of the left subclavian artery (Fig. 4).

Correction was performed on July 16, 1973 through a left thoracotomy. The stenotic area was proximal to the ligamentum arteriosum and involved the take-off of the left subclavian artery. Aortic cross-clamping, including the subclavian, resulted in a mean pressure of 35 mm Hg in the distal thoracic aorta. A heparin-coated temporary shunt was then placed from the ascending aorta to the left external iliac artery. With bypass established, and the aorta occluded, distal pressure was maintained at 90/70 mm Hg. No elevation of proximal blood pressure occurred, and urinary output was satisfactory. The coarctation was excised and an end-to-end anastomosis accomplished. The patient's postoperative course was uncomplicated. He has remained normotensive with full peripheral pulses. He is free of symptoms and fully active.

Discussion

Resection and primary anastomosis can be accomplished in most patients with coarctation of the thoracic aorta without the need for bypass. However, aortic cross-clamping introduces the hazards of catastrophic proximal hypertension[5] and insufficient distal circulation to protect the spinal cord.[11] This morbidity is directly related to the adequacy of the collateral circulation. Brewer *et al.*[4] have

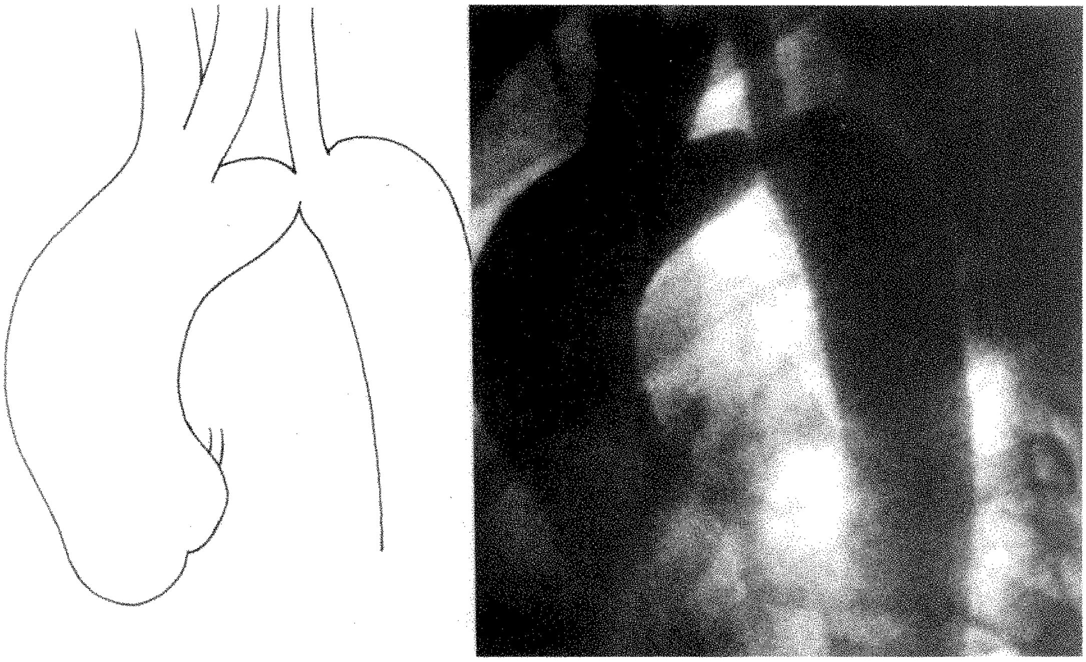

FIG. 2. Aortogram and line drawing illustrating coarctation of the thoracic aorta proximal to the origin of the left subclavian artery.

emphasized that preparation must be made for left heart bypass, hypothermia, or jump graft in any case of coarctation with evidence of inadequate collateral circulation. This high risk group includes: 1) patients with palpable femoral pulses and lack of hypertension in the upper extremities; 2) patients who require a second operation; and 3) patients with aneurysm at the site of the coarctation or one of the intercostal arteries.

Coarctation of the aorta proximal to or involving the left subclavian artery presents a similar risk. Evidence of collateral circulation is usually minimal and is limited to the right side.[10] Also, occlusion of the left subclavian at the time of resection is usually necessary. Adams *et al.*[1] have stressed that danger to the cord exists if the coarctation is proximal to the subclavian artery. Hughes and Reemtsma[11] have emphasized that intraoperative measurement of distal aortic pressure before and after test occlusion may provide an objective indication of the adequacy of collateral circulation. If the distal aortic pressure falls below a mean of 50 mm Hg, left atrial-femoral artery bypass has been utilized. In the present report, aortic occlusion lowered the distal pressure to a critical level and indicated the necessity for bypass. Catastrophic proximal hypertension may occur when the aorta is cross-clamped.[2] The first patient described herein developed intolerable elevation of the central blood pressure with aortic occlusion. The second patient did not develop proximal hypertension, but was unable to maintain a satisfactory pressure in the distal aorta. In both cases, a heparin-coated temporary shunt provided a simple and effective method of management.

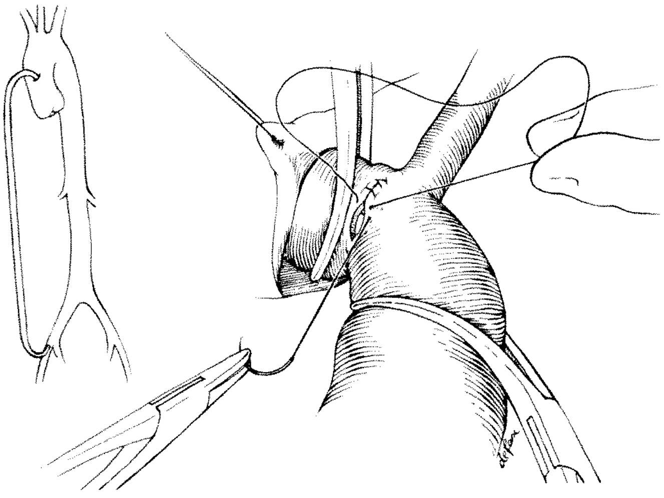

FIG. 3. End-to-end anastomosis is completed following excision of the coarctation. Inset illustrates placement of the heparin-coated shunt bypass from ascending aorta to external iliac artery.

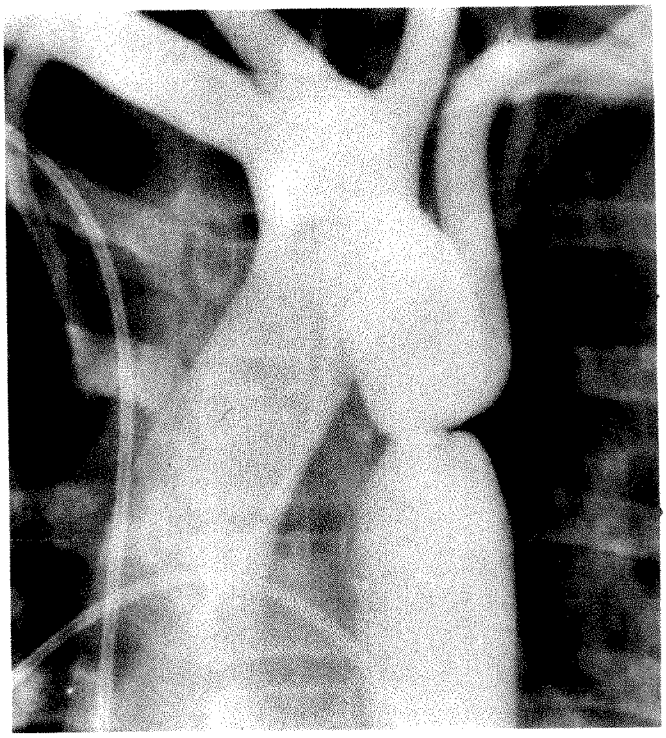

FIG. 4. Thoracic aortogram demonstrating coarctation of the aorta involving the origin of the left subclavian artery.

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Visceral Infarction Following Aortic Surgery

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An experience with aortic surgery is reported which reveals that visceral ischemia is more frequent than expected and significantly contributes to operative mortality. Two of five deaths among 84 patients who had aorto-iliac occlusive disease and four of 40 deaths among 103 aneurysmectomies (both ruptured and elective) were related to visceral ischemia. A review of the literature reveals 99 cases of colonic ischemia in more than 6,100 cases of aortic surgery, an incidence of 1.5%. Only 10 cases of small bowel ischemia were recorded. The present experience with 9 cases of colon ischemia and one of small bowel ischemia is presented particularly with reference to pathophysiology and prevention. It is concluded that patients should be identified by appropriate angiography if considered a risk for visceral infarction, and, if present, visceral arterial reconstruction should be performed in addition to aortic reconstructive surgery. Colon infarction following aortic aneurysmal surgery is directly related to ligation of a patent IMA. Thus re-implantation of the patent IMA should be considered.

WITHIN THE PAST DECADE, refinements in operative technique, anesthetic management, prevention and reatment of renal failure and sophistication in respiraory therapy have contributed to the progressive decrease n operative mortality of aortic surgery. However, alhough vascular insufficiency of the gastro-intestinal tract ollowing aortic surgery is relatively uncommon, it repesents an area where improvement in management may urther add to the reduction in operative mortality.

This report consists of nine cases of visceral infarction, oth small and large bowel, following surgery of the ablominal aorta. An analysis of these cases, together with review of the literature illustrates the frequency and ignificant of visceral infarction and affords a prospective n the proper surgical management of this condition.

Case Reports

Group A. Small Bowel Ischemia

Case 1. In October of 1971, a 62-year-old male underwent an aortic bilateral iliac endarterectomy and (R) sympathectomy for intermittent claudication of the right calf. In July 1972, he was admitted for severe pain in the left leg on minimal exertion. Physical examination revealed the absence of both femoral pulses. There was no skin necrosis. Aortogram revealed severe stenosis of the abdominal aorta, occlusion of the left common iliac artery, and stenosis of the right common iliac artery. Additionally, severe stenosis or occlusion of the superior mesenteric artery was suspected because of a large gastroduodenal artery that filled the superior mesenteric circulation. The inferior mesenteric artery was small and the left colic branch was easily identified (Fig. 1a). At surgery a 16 mm knitted DeBakey Dacron bypass graft was anastamosed to the aorta just distal to the left renal artery, and to the left common femoral artery and right external iliac artery (Fig. 1b). The patient was well until the eight postoperative day when he began complaining of vague abdominal and back pain and developed abdominal distention and gastric retention. On the following day the patient was found to be hypotensive. Blood and fluids were administered with elevation of his central venous pressure to 18 cm of water. However, his systolic pressure remained low, in the range of 60 to 80. It was noted that the patient had no sensation from the waist down and was unable to move his legs. At this time each femoral artery had a good pulsation present within it. The patient continued to be unresponsive to all supportive therapy and died. Autopsy revealed the cause of death as a mesenteric infarction. Both the small bowel and right colon were infarcted. Examination of the aorta revealed a totally occluded superior mesenteric artery and a recent thrombosis of the aorta distal to the take off of the aortic bifurcation graft and extending into each common iliac artery. The celiac artery was normal appearing with an adequate lumen. The neurological deficits may have been secondary to an infarction of the spinal cord caused by thrombosis of the bypassed lumbar arteries. Histopathology of the spinal cord was not performed, nor were the radicular arteries identified.

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Group II. Colon Ischemia Following Elective Aneurysmectomy

Case 2. A 76-year-old male with severe angina was admitted with lower abdominal pain and was found to have an 8 cm abdominal aneurysm. He underwent resection of the aneurysm and insertion of a Teflon prothesis. The IMA was ligated. On the ninth day postoperatively the patient had some watery diarrhea, and on the 19th post-op day he developed extensive rectal bleeding and was hypotensive; emergency laparotomy revealed extensive necrosis of the colon (from splenic flexure to the rectum). A resection of the necrotic colon was performed and a proximal colostomy was established. The patient died in the immediate post-operative period in the state of irreversible shock despite all supportive measures. No post mortem examination was performed.

Case 3. A 60-year-old man entered with back pain that began two months prior to admission. On exam, he was found to have a 5 cm aortic aneurysm. He underwent an elective resection of this aneurysm with Teflon graft replacement. Postoperatively, he developed renal impairment and prolonged ileus and sepsis and died on his 13th post-op day. Post mortem revealed extensive peritonitis (3000 cc purulent fluid). No gross perforation of the gastrointestinal tract was found; however, microscopic examination of the colon revealed chronic non-specific inflammatory reaction of the wall of the bowel possibly consistent with ischemia.

Group III. Colon Ischemia Following Emergency Aneurysmectomy

Case 4. A 68-year-old male was admitted in 1959 with severe back pain and a known abdominal aneurysm. Physical exam revealed BP 150/80 and a tender pulsatile mass. Emergency laparotomy revealed a leaking abdominal aneurysm that extended from the renal arteries to each external iliac artery. The aneurysm was resected and a Dacron prosthetic graft was inserted. The operative dissection was difficult and there was extensive bleeding of venous origin. The vena cava was ligated 5 cm below the renal veins, the internal iliac veins were also ligated. The patient remained relatively stable until the second post-op day when he developed severe respiratory impairment and died. Post mortem findings revealed pulmonary congestion, aspiration pneumonia, superior mesenteric venous thrombosis and acute infarction of the ascending colon, sigmoid and rectum.

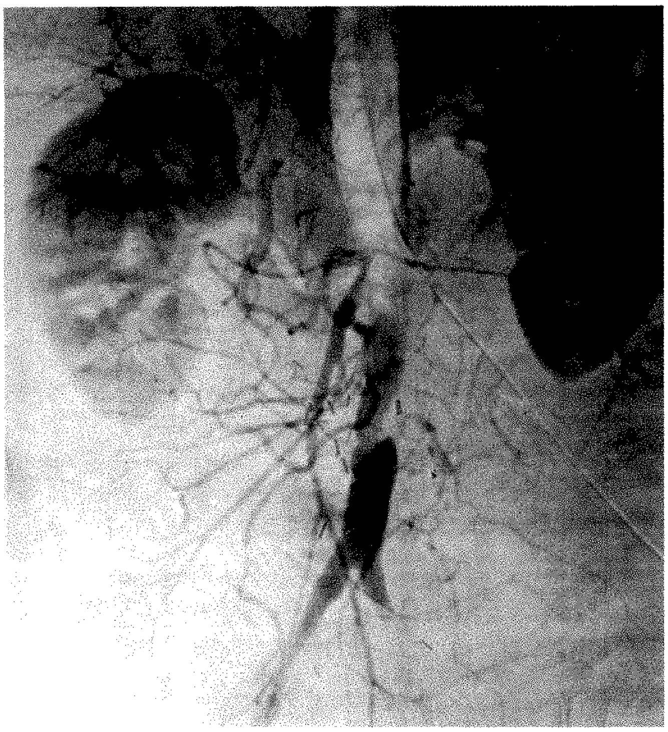

FIG. 1a. "Substraction" aortography of case 1 showing the stenosis of the abdominal aorto, occlusion of the left common iliac artery and stenosis of the right common iliac artery. Additionally, severe stenosis or occlusion of the SMA was suspected because of a large gastroduodenal artery that filled the SMA. The IMA was small and L colic artery is easily seen.

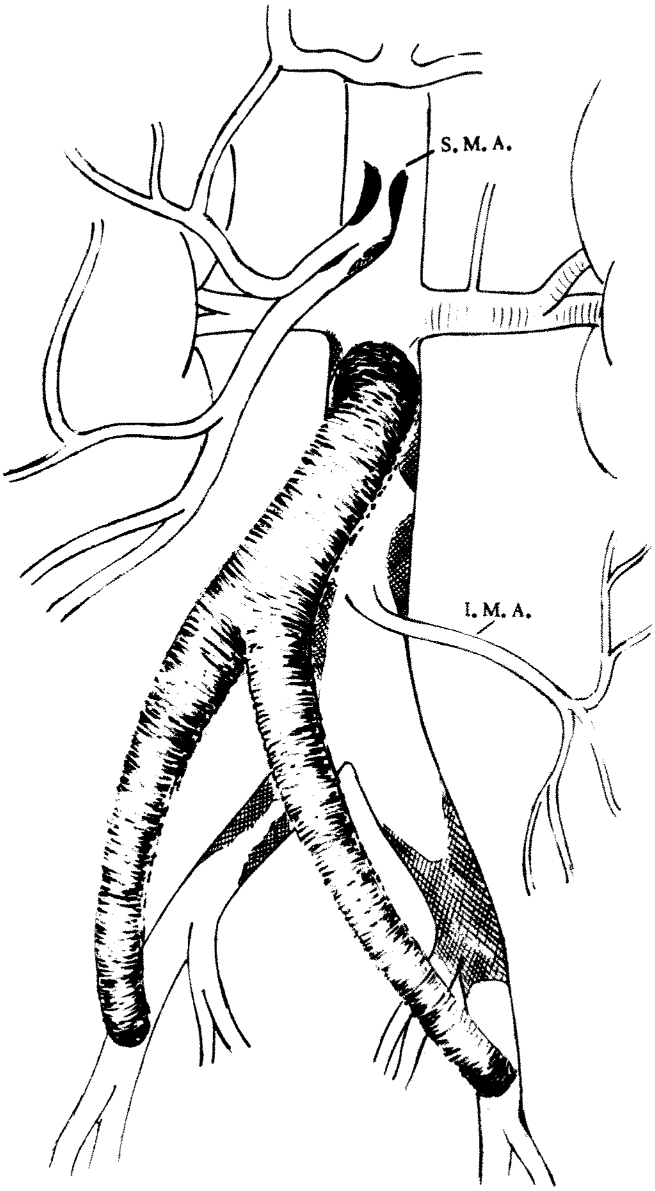

FIG. 1b. Representation of arterial occlusive disease in case 1 and the operative repair of an aorto-bilateral femoral bypass.

Case 5. A 77-year-old male with previous arteriosclerotic heart disease was admitted with sudden and severe abdominal pain. On physical exam he was found to be severely hypotensive and had a pulsatile abdominal mass. Emergency laparotomy revealed a ruptured abdominal aortic aneurysm, which was resected and a dacron prosthesis was inserted. His inferior mesenteric artery was ligated. At the completion of the operative procedure he was normal tensive and the bowel grossly looked normal. Four days after surgery, hemodialysis was begun for progressive renal failure. On the sixth postoperative day he developed postoperative respiratory insufficiency requiring tracheostomy and mechanical ventilation. At the same time he developed tenderness in the left lower abdomen, and sigmoidoscopy revealed necrotic, greyish-brown mucosa of the entire rectum. His poor general condition precluded operative intervention. He remained on a gradual downhill course and died on the 9th post operative day. No post mortem was obtained.

Group IV. Colon Ischemia Following Aortoiliac Reconstructive Surgery

Case 6. A 48-year-old male was admitted because of intermittent claudication of two to three years duration associated with impotence during the past year. Physical examination revealed no palpable pulses in the left femoral area or distally, the right leg had a palpable femoral pulse but weak pedal pulses. Aortography showed a localized block of the left iliac artery. The patient underwent a Dacron graft bypass from the distal portion of the aorta to the left external iliac artery with a bilateral sympathectomy. In the postoperative period, the patient began having a cool left foot, and was complaining of severe paresthesia. In addition, he began complaining of pain in his right calf and thigh and on physical exam there was no left femoral pulse and only a weak right femoral pulse. The patient underwent re-exploration with insertion of a aortic bifurcation graft, extending from the aorta at a point just below the renal arteries to the left common femoral artery and the right external iliac. The distal transected abdominal aorta was ligated distally and the inferior mesenteric artery had previously been ligated. Postoperatively the patient had good return of blood flow to both the lower extremities and did well in regard to his vascular reconstruction. However, he began developing intermittent episodes of fever, severe diarrhea, and lower abdominal pain. Sigmoidoscopy was normal. A barium enema revealed a stenotic area in the sigmoid colon that was compatible with ischemic colitis and the patient underwent transverse colostomy. Two months later, laparotomy revealed an ileosigmoid fistula and a stenotic sigmoid colon. He underwent resection of the diseased sigmoid colon. The pathology specimen revealed an acute and chronic inflammation of the large intestines with evidence of necrosis that was transmural. At the time of sigmoid resection it was also noted that there was a small abscess or necrotic area adjacent to the old aortic graft and for this he was placed on massive doses of penicillin in the postoperative period. Two months later, the patient was readmitted with bleeding from his colostomy. Associated with this was severe abdominal pain and pain in his back. A possible aortic duodenal fistula was considered and he was transfused and placed on bed rest. The following morning he suddenly became worse with hypotension, abdominal swelling, and severe abdominal pain. Emergency laparotomy confirmed an aorto-duodenal fistula

TABLE 1. *Colon Ischemia Following Aortic Surgery*

Author	Year	Local	Patients at Risk	Total Number of cases AAE/AAR/AIO	Number Deaths related to Ischemia AAE/AAR/AIO	Type of Injury *A* Mucosal Injury	*B* Muscularis Injury (stricture, obstruction)	*C* Transmural Necrosis	
Moore[16]	1954	N. Y. Hosp.	7	1–0–0	0–0–0	0	1	0	
Cannon[29]	1955	Los Angeles	15	1–0–0	1–0–0	0	0	1	(1)
Movius[18]	1955	Long Beach	10	2–0–0	0–0–0	0	2	0	
Barnes[1]	1958	Mayo Clinic	78-AA	1–0–0	1–0–0	0	0	1	(1)
			70 AIO	0–0–0	0–0–0		0	0	
McKain[14]	1958	U. Indiana	—	2–0–0	1–0–0	0	1	1	(1)
Smith[24]	1960	Henry Ford	120 AA	7–4–0	2–1–0	4	4	3	(3)
Bergantz[2]	1960	Mayo Clinic	400 AA	4–0–0	4–0–0	0	0	4	(4)
Ochsner[19]	1960	Houston	931 AA	0–2–0	(?)	0	0	2	(?)
Perdue[21]	1962	Atlanta	—	3–1–0	1–1–0	1	1	2	(2)
Bernstein[3]	1963	U. Minn.	200 AA	3–1–0	1–1–0	1	1	2	(2)
Young[29]	1963	Cleveland	800	0–4–2	0–3–1	0	0	6	(4)
Birnbaum[5]	1964	U. of Calif.	250 AA	4–0–0	1–0–0	1	2	1	(1)
		San Francisco	900 AIO	0–0–1	0–0–1	0	0	1	(1)
Miller[15]	1968	Milbourne	—	2–0–0	0–0–0	0	2	0	
Bicks[4]	1968	U. Tenn.	17 Years	17–2–0	8–1–0	8	0	11	(9)
Gibson[8]	1969	Tulane	600	1–0–0	1–0–0	0	0	1	(1)
Sweetman[26]	1969	Portland	—	2–0–0	0–0–0	2		0	
Sher[23]	1970	Framingham	—	0–0–1	0–0–1	0	0	1	(1)
Hardy[10]	1971	U. Miss.	400 AA	1–1–0	0–0–0	1	1	0	
Ottinger[20]	1972	MGH	1200	4–9–7	1–2–1	5	2	13	(4)
Johnson	1973	Boston VA	103 AA	2–5–0	2–2–0	3	0	4	(4)
			84 AIO	0–0–2	0–0–1	0	1	1	(1)
			6168	57–29–13 –99–	24–11–5	26 (0)	18 (0)	55	(40)

AAE = Aortic Aneurysm Resection Elective.
AAR = Aortic Aneurysm Resection Ruptured.
AIO = Aortic Iliac Occlusive Disease.
Numbers with ( ) represent death directly related to bowel ischemia.

with disruption of the proximal anastomoses of the aortobifurcation graft, the patient expired during the operation.

Group V. Patchy Small and Large Bowel Ischemia Following Aortic Surgery

Case 7. Fifteen months previously, this 74-year-old white man had an elective abdominal aortic aneurysmectomy. One year later he was admitted with an aortic duodenal fistula, for which he had closure of the fistula and repair of the duodenum (without removal of the graft). He was discharged from the hospital only to be admitted two weeks later with recurrent hemetemesis. Because of the recurrent aorto-duodenal fistula the Dacron aortic graft was removed, the abdominal aorta was oversewn and a (R) axillo-bilateral femoral bypass was established. He died four days postoperatively from a clinically diagnosed cardio-respiratory insufficiency. The post mortem showed: cardiomegaly, pulmonary broncho pneumonia; and multiple focal infarctions of the colon and small bowel.

Case 8. A 69-year-old man was admitted in December 1960 with hypotension and an abdominal aneurysm. He refused surgery, slowly improved and was discharged. Eight months later, he was re-admitted with LLQ pain and a mass. At surgery he was found to have a 15 cm wide aortic aneurysm. This was resected and a Teflon bypass graft inserted. The inferior mesenteric artery was noted to be occluded. The (L) kidney preoperatively had not been functioning. Postoperatively, the patient developed acute renal failure and died suddenly on his second postoperative day. Autopsy revealed extensive coronary artery occlusive disease and an old myocardial infarct, and acute occlusion of the right renal artery. In addition, patchy areas of beefy red mucosa in the ileum, descending colon and recto sigmoid were found. On microscopic examination these areas showed a complete loss of epithelium, consistent with ischemia, but no perforations were apparent.

Case 9. A 71-year-old man was admitted with hypotension and a left flank mass. Emergency surgery revealed a ruptured aneurysm, which was resected. Postoperatively, he was hypotensive and died in his second postoperative day. Autopsy revealed cardiomegaly and an old myocardial infarct, a thoracic aneurysm; and a carcinoma of the cecum. Also noted were patchy black-red areas throughout the small intestine and colon suggestive of early focal gangrene. The SMA was patent.

Discussion

In this series, visceral ischemia developed in two of 84 patients following surgery for aortic occlusive disease, and seven of 103 patients following aneurysmal surgery. In a review of the literature plus our series, 20 authors reported 99 cases of colonic ischemia in over 6300 cases of abdominal aortic surgery, (86 cases were following aneurysmectomy) an overall incidence of about 1.5% (Table 1). Forty per cent of these patients died. No mortality was associated with mucosal, or mucularis ischemia, however, with transmural necrosis it was the cause of death in 40 of 55 patients.

Most authors did not state the relative risks of colonic infarction following the different aortic procedures. However, considering those authors who did, the risk following aneurysmectomy was 34 of 2394 (1.4%) with an associated mortality of 48%. Following reconstructive procedures for aorto iliac occlusive disease, the incidence was only 3 of 1054, all of which died.

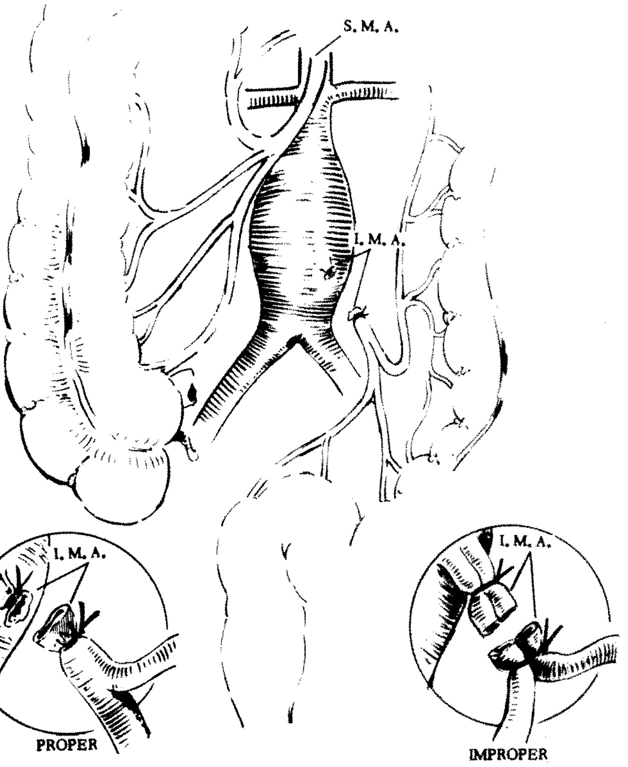

FIG. 2. The inferior mesenteric artery branches into the left colic artery (LCA) and superior sigmoidal artery (SSA), ligation of the IMA close to the aorta will preserve collateral circulation between the LCA and SSA, however, improper ligation of the IMA will obliterate this collateral circulation.

The most apparent cause for the colonic ischemia appears to be the sacrifice of the inferior mesenteric artery. Why this should lead to ischemia in only certain patients is related to variation in collateral blood supply. Griffiths has reported that 20% of patients may lack a middle colic artery.[9] Additionally, the marginal artery of Drummond may not always be continuous; i.e., it is said to be lacking in the region of the ascending colon in about 5% of individuals; in the region of the sigmoid in 20% and at the recto-sigmoid junction much more often.[25] As shown in Fig. 2 improper ligation of the IMA away from the aorta may obliterate the anastomotic collateral circulation from the descending colon to the sigmoid colon. Arteriosclerotic involvement of the SMA and internal iliac arteries will also lead to poor collateral circulation.

The clinical syndromes associated with colonic ischemia are extremely variable and relate to the colonic pathologic process. Colonic mucosal injury usually leads to only diarrhea and usually is self limiting. Colonic mucosal and muscularis injury leads to bloody diarrhea and occasional fever and subsequently to stricture forma-

TABLE 2. *Small Bowel Ischemia Following Abdominal Aortic Surgery*

Author	Year	Institution	Patients at Risk	Death	Aortic Disease	Ischemic Etiology	Comments
Barnes[1]	1958	Mayo Clinic	150	Yes	AAR	SMA occlusion IMA sacrificed	Following resection of an abdominal aortic aneurysm and homograft replacement, the patient developed gangrene of the entire large and small bowel, autopsy revealed SMA occlusion.
Kountz[11]	1966	Stanford	—	Yes	AOD	"mesenteric steal"	Following aortic bilateral femoral bypass and sympathectomy. The patient developed "intestinal angina", angiography revealed mesenteric vascularization via the IMA and a large central meandering anastomic artery. During preparation for corrective surgery he developed patchy infarction of the ilium from which he died.
Young[29]	1967	Clev. Clinic	—	Yes	AOD (2 patients)	insufficient information	The day following surgery for aortic occlusive disease, the two patients developed intestinal infarction (small and large bowel in one, only small bowel in the other) with resultant death.
Lancaster[12]	1967	W. Vir. VA	—	Yes	AOD	"mesenteric steal"	On 3rd day after aorto iliac Dacron replacement, emergency laparotomy revealed a mesenteric infarction. Autopsy revealed stenosis of the SMA, IMA, and iliac arteries. Retrospectively, it was apparent that his preoperative ulcer complaint was really intestinal angina.
Williams[28]	1968	BCH	—	Yes	AOD	"steal syndrome"	A patient who previously had a left sympathectomy, developed abdominal pain, vomited, aspirated and died three days after aortic left iliac bypass. Post mortem revealed patchy infarction of the proximal jejunum, and total occlusion of the SMA and celiac artery.
Seltzer[22]	1969	U. Penn.	15 yrs.	Yes	AAR (2 patients)	SMA occlusion IMA sacrificed	Following abdominal aortic aneurysmectomy, mesenteric infarction occurred and autopsy revealed superior mesenteric arterial occlusion.
Foster[7]	1971	Nashville	—	No	AOD	collaterals sacrificed	An 8 yr. old boy had severe left renal arterial stenosis, severe stenosis of the SMA, and occlusion of the iliac artery. Postoperatively following aorto-renal arterial bypass (using the left hypogastric artery) severe abdominal angina developed, requiring revascularization of the SMA.
Trippel[27]	1972	Chicago	60	Yes	AOD	"mesenteric steal"	12 hours following bilateral aorto femoral bypass and bilateral lumbar sympathectomy, the patient became hypotensive; rapidly deteriorated and died within 25 hours of operation. Autopsy revealed thrombosis of the SMA with massive intestinal infarction.
Johnson	1972	Boston VA	187	Yes	AOD	Retrograde thrombosis of bypassed aorta with IMA occlusion	On the 8th postoperative day following aortic-bilateral femoral dacron bypass symptoms of visceral infarction developed. Autopsy revealed an occluded SMA, a thrombosis of the iliac arteries and aorta associated with secondary occlusion of the IMA.

AOD = Aortic occlusive disease.
AAR = Aortic aneurysm (ruptual)
SMA = Superior mesenteric artery.
IMA = Inferior mesenteric artery.

tion. In contrast, colonic infarction usually has an early postoperative appearance, manifests itself by fever, shock, and bowel perforation, usually leading to death if unrecognized early. The ability to recognize the various clinical states is dependent on thinking of such a possibility and then making a definitive diagnosis by sigmoidoscopy, colonoscopy or Barium enema. Proctoscopic examination will reveal a cynanotic, friable, and often ulcerative mucosa.

Small bowel ischemia following abdominal aortic surgery is much less frequent than colonic infarction. Review of the literature reveals that 10 cases have been reported, about 1/10 as often as colonic ischemia has been reported (Table 2). The incidence is estimated at about 0.15% of aortic cases. However, in contrast to colonic ischemia, most (7 patients) developed small bowel ischemia following surgery for aortic occlusive disease; with an associated mortality of 90%.

The pathophysiological changes that explain small bowel ischemia may be several fold. Kountz reported in 1966 a case of small bowel infarction that he explained as a sequalae of a steal phenomenon of the mesenteric circulation following reconstruction of the aorta with lumbar sympathectomy in a patient with aorto iliac occlusive disease. He also presented laboratory evidence that supported the concept that sympathectomy plus revascularization of the extremities led to a 40–70% decrease in mesenteric flow.[11] It is apparent from the several other cases reported that this "steal phenomena" may cause small bowel ischemia in patients who have a stenotic SMA and receive retrograde flow via the IMA.[12,27,28] Secondly, in patients with a stenotic SMA the occlusion of the IMA either at the time of surgery or by thrombosis of the "bypassed" aorta may lead to insufficient collateral flow to the small bowel as reported in case one.

Clinically, the symptoms of small bowel ischemia may vary from the signs of severe shock and refractory hypotension associated with generalized mesenteric infarction, to the nausea and vomiting and vague abdominal pain seen prior to perforation when patchy infarction has occurred, or to only postprandial intestinal angina with mild ischemia.

Prevention

Postoperative visceral insufficiency is a significant complication with an associated mortality of 40% with colonic ischemia and 90% with small bowel ischemia. It is apparent that prevention is the preferred mode of therapy. The present operative mortality for elective abdominal aneurysmal surgery is 3–7%.[6] However, if approximately 0.4% of patients having aortic surgery are dying from ischemic bowel difficulties, then 10% of the operative mortality associated with elective aortic aneurysmal surgery is secondary to bowel infarction. It is in this fraction of the operative mortality that preventive concepts should be developed.

Patients who are at "high risk" for post operative visceral ischemia must be detected. A history suggestive of intestinal angina or physical findings of abdominal bruits make appropriate angiography necessary. However, the authors believe that routine aortic angiography is justified solely because of the risk of visceral ischemia in patients undergoing aortic surgery, either aneurysmal or reconstructive. Additional benefits of angiography in aneurysmal patients is the determination of multiple renal arteries or other vascular abnormalities. Angiography should include lateral films to visualize the SMA and celiac origins. A large meandering mesenteric artery is indicative of an occlusive process in the superior or inferior mesenteric artery. However in patients with only a severe stenosis such collateral circulation may not be

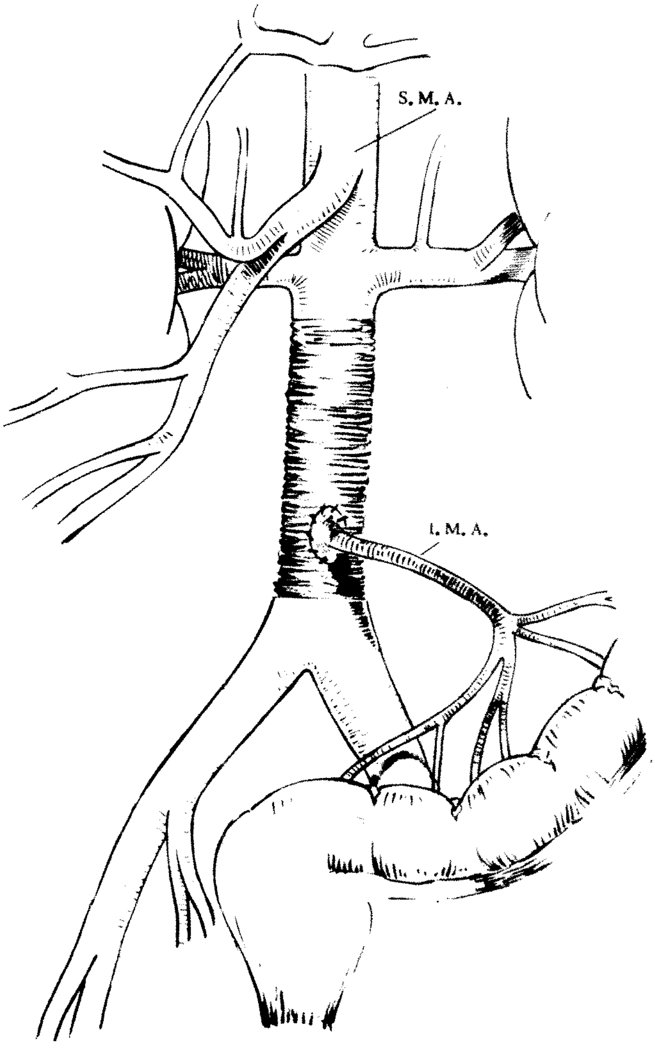

FIG. 3. Technique of revascularization of the inferior mesenteric artery by direct re-implantation into the aortic prosthesis. (Note that when the IMA was detached from the aneurysm that a cuff of aorta was preserved to allow an easier anastomosis).

developed. Several situations where prophylactic reconstruction may be justified are:

1. The SMA is stenotic and receives collateral circulation through a meandering artery from the IMA. Sacrifice of the IMA would probably lead to small bowel ischemia and should be preserved or reimplanted into the aortic graft (Fig. 3). Alternatively, a bypass from the aortic prosthesis to the SMA could be performed.

2. The IMA is patent, however, the internal iliac arteries are stenotic. Sacrifice of the IMA may lead to colonic ischemia and should be preserved or reimplanted into the aortic graft.

3. Patients who have bypass procedures beginning proximal to a patent IMA may develop thrombosis of their aorta leading to occlusion of the IMA and implantation of the IMA into the aortic prosthesis should be considered.

4. The IMA is occluded. As shown in Fig. 2, if one is to ligate the IMA during aneurysmectomy this should be done immediately adjacent to the aorta to preserve the collateral circulation between the left colic artery and the sigmoid arteries. However, it may be preferable to remove a cuff of the aorta with the IMA and if, as may be present in a partially thrombosed aneurysm, a small thrombus can be liberated resulting in good back bleeding the IMA can be transplanted to the aortic prothesis as in Fig. 3.

5. Patent IMA and normal vasculature. These patients are not at as high a risk as those with occluded internal iliacs, but colon ischemia has followed sacrifice of the IMA, most likely because of incontinence of the marginal artery of Drummond. Thus the reimplantation of a patent IMA during aneurysmectomy should be considered.

The recent introduction of a new dacron aortic bifurcation graft that has a 6mm limb attached to the aortic portion has simplified revascularization of the SMA or IMA.* Thus revascularization may be performed without the need for occlusion of the aortic prothesis.

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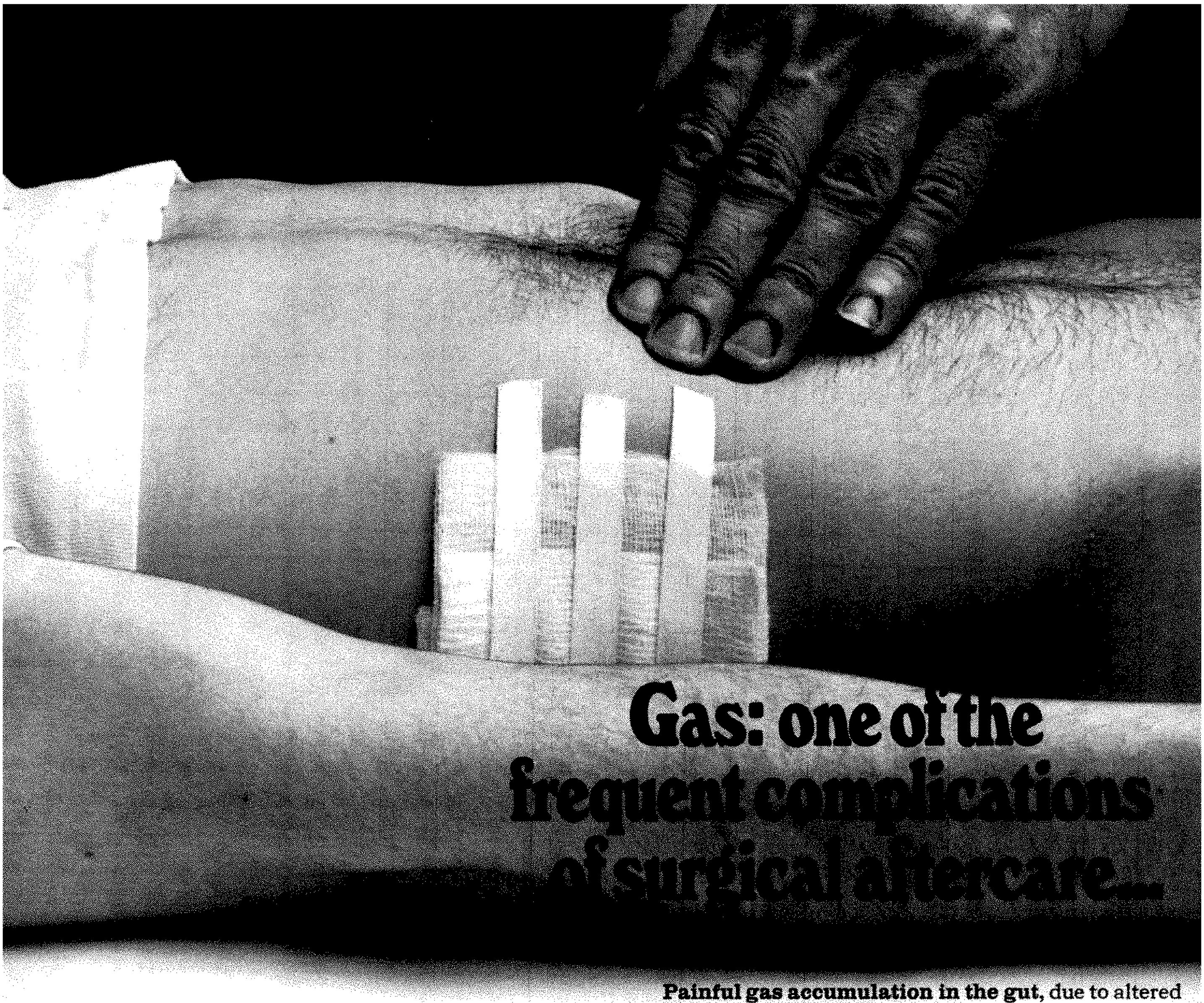

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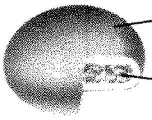

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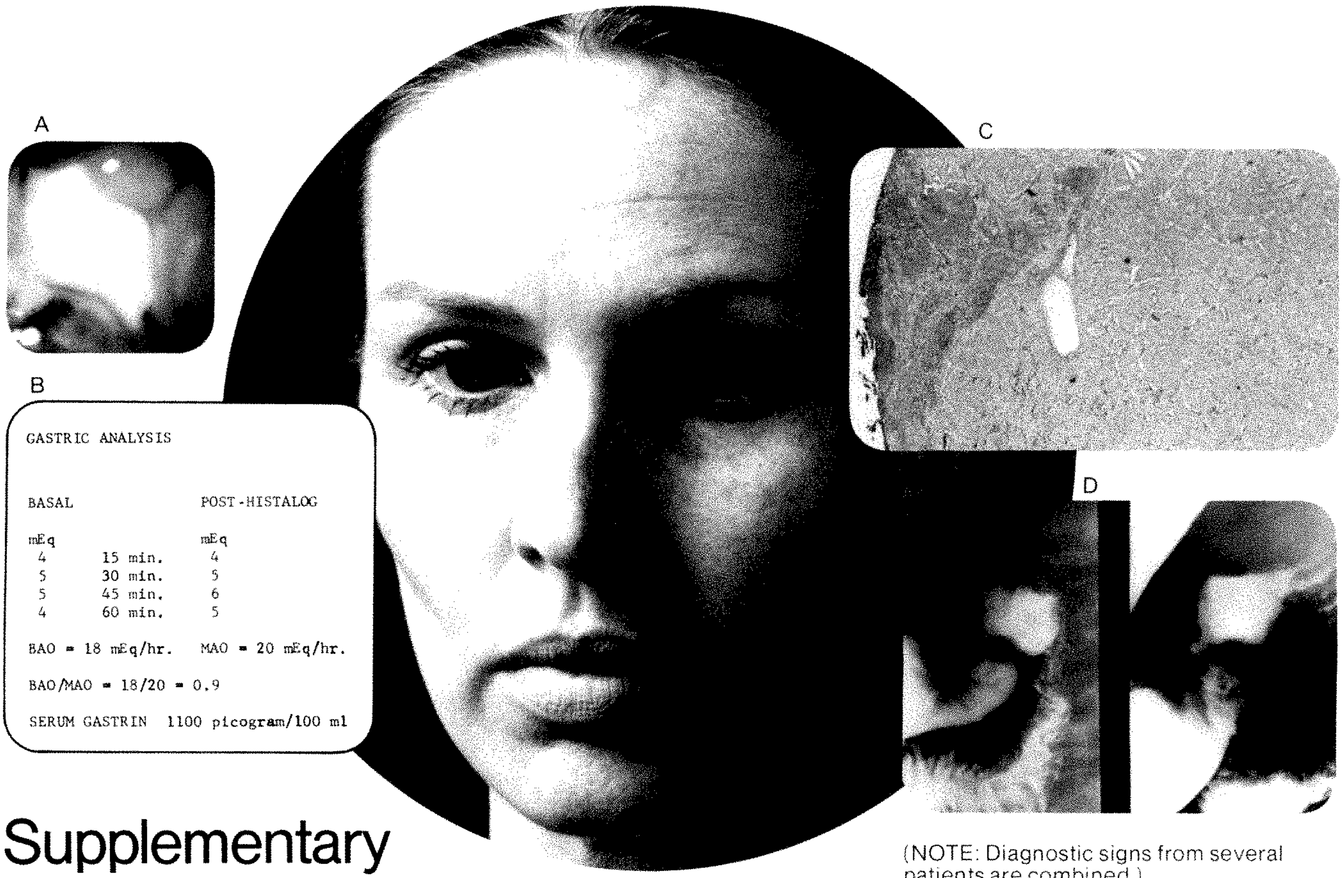

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5	30 min.	5
5	45 min.	6
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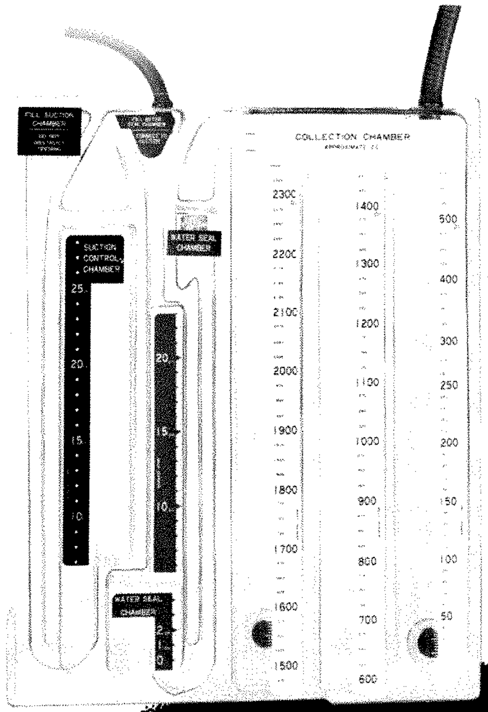

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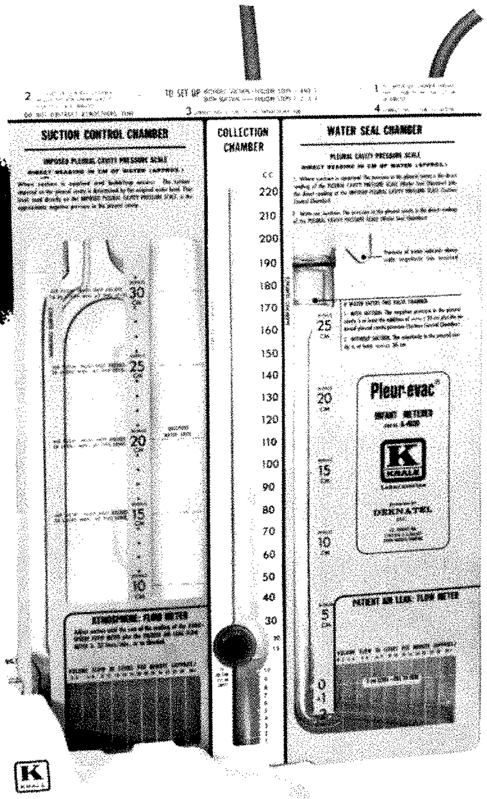

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Lymphoid Polyposis Associated with Familial Polyposis and Gardner's Syndrome

LONNIE N. SHULL, JR., M.D.,* CHARLES T. FITTS, M.D.†

This report describes a family with familial polyposis and lymphoid polyps in which a single member exhibits features of Gardner's Syndrome. A review of the literature pertaining to the simultaneous occurrence of lymphoid polyposis with Gardner's Syndrome and familial polyposis is presented. The importance of histologic diagnosis is stressed.

From the Department of Surgery, Medical University of South Carolina, Charleston, South Carolina

FAMILIAL POLYPOSIS and Gardner's Syndrome are diseases of recognized surgical significance. Both disorders are characterized by a high incidence of carcinoma developing in the large bowel and for which the present acceptable surgical treatment is total colectomy. Lymphoid polyposis, on the other hand, is a benign disorder which may be less familiar to the surgeon. Recognition of the benign nature of this disorder is important in order to differentiate it from familial polyposis and Gardner's Syndrome. Recent reports, however, have noted the simultaneous occurrence of florid lymphoid polyps in patients with familial polyposis and in Gardner's Syndrome. As yet, the significance of this finding is not well understood. This report describes a family with familial polyposis in whom both lymphoid polyps and features of Gardner's Syndrome have been found.

Family History

A family tree of the propositus is presented in Fig. 1. The patients' father had a 20-year history of rectal bleeding and underwent total colectomy for multiple polyposis. An older brother had undergone total colectomy for carcinoma at age 33. Two younger brothers have had total colectomy for multiple colonic polyps. Four other siblings have been studied and no evidence of colonic polyps has been found. A single sibling died in infancy. There is no known history of consanguinity.

Case Report

A 29-year-old Caucasian male was admitted to the Medical University Hospital in 1969 with a history of bloody diarrhea for one year and the recent onset of fever and malaise. His previous history included an operation for peptic ulcer disease four years prior to admission and resection of an abdominal wall tumor the following year. Proctosigmoidoscopy and barium enema revealed extensive colo-rectal polyps which on biopsy were shown to be adenomatous polyps. Subtotal colectomy and ileo-proctostomy were performed in August, 1969. Examination of the surgical specimen revealed a myriad of small adenomatous polyps, a large pedunculated polyp, and a villous adenoma (Figs. 2 and 3). The distal 40 cm of ileum was sigmoidoscoped at surgery and was found to contain numerous small lymphoid polyps. His postoperative course was complicated by intestinal obstruction necessitating re-operation and lysis of adhesions. In 1970, excision of a second abdominal wall tumor was performed and on histologic examination proved to be a desmoid. One year after his colectomy, recurrent symptoms related to the remaining rectal polyps necessitated protectomy and ileostomy which was performed uneventfully. Microscopic examination of the surgical specimen revealed multiple benign lymphoid polyps of the terminal ileum and rectum (Fig. 4). No additional adenomatous polyps were found in the rectal specimen. More recently the patient has had excision of a sebaceous cyst of the right temporal region. Skeletal films have failed to demonstrate any bony abnormalities of the mandible or skull.

Discussion

Multiple lymphoid polyposis of the gastrointestinal tract has been well documented since its original de-

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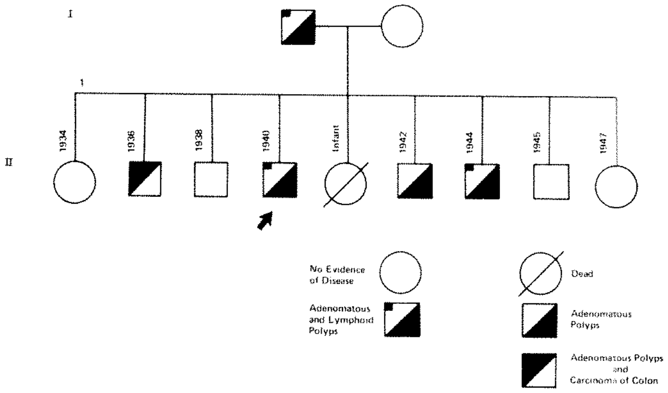

FIG. 1. Family tree with propositus indicated by arrow.

scription by Briquet in 1838.[2,4,14,17] It is now recognized as a benign condition consisting of aggregates of hyperplastic submucosal lymphoid follicles.[2,12] The condition is most frequently recognized in children or adolescents,[1,2] and can be suspected from its radiographic appearance.[15,18] Presenting symptoms are usually mild and consist of alternating diarrhea and constipation with the occasional passage of blood. A tendency toward spontaneous regression of the polyps has been well documented in several cases.[1,2,9] Recognition of this disease by the surgeon is of importance from two standpoints. First, the condition can produce such symptoms as bleeding, intussusception, or intestinal obstruction which necessitate surgical intervention.[13] Secondly, laparotomy may be necessary to differentiate this condition from familial polyposis and Gardner's Syndrome.

The need for histologic confirmation of the diagnosis is especially important since the recognition that benign lymphoid polyposis can co-exist with both familial polyposis and Gardner's Syndrome. In 1968 Thomford and Greenberger reported a case in which lymphoid polyps of the terminal ileum were found at the time of colectomy in a patient with Gardner's Syndrome.[16] A similar finding was reported in two patients with familial polyposis in 1970[3] More recently, another case was reported in which there was a definite history of familial polyposis, but at the time of colectomy, only lymphoid polyps were found.[6]

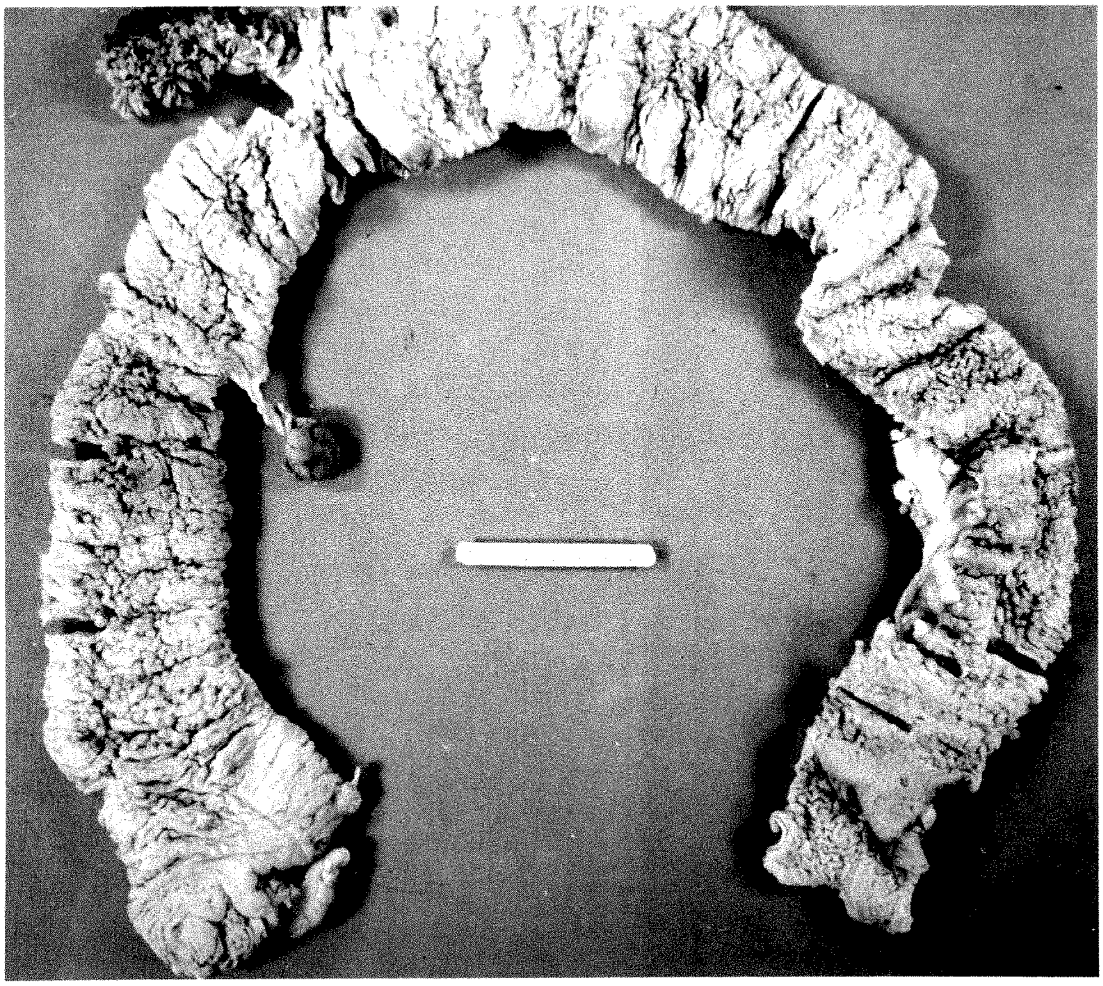

FIG. 2. Subtotal colectomy specimen showing small adenomatous polyps, a large pedunculated adenomatous polyp and villous adenoma. Several small lymphoid polyps can also be seen in the terminal ileum.

Several of the family members in our pedigree had lymphoid polyps of the terminal ileum in addition to adenomatous colonic polyps (Fig. 1). However, the finding of lymphoid polyps and features of Gardner's Syndrome in the propositus is extremely interesting. Familial occurrence of lymphoid polyposis has been described,[2,9] but the simultaneous occurrence of familial polyposis and Gardner's Syndrome in the same family has not been previously reported.[10] Both are inherited in an autosomal dominant fashion and are thought to be controlled by separate genes, although the possibility of the genes being allelic has been considered.[11]

The significance of simultaneous occurrence of lymphoid polyposis of the bowel with both Gardner's Syndrome and familial polyposis is not well understood at present. Gruenberg and Mackman suggest that multiple lymphoid polyps may represent another manifestation of familial adenomatous polyposis.[6] Isolated case reports of carcinoma and lymphoma occurring in association with lymphoid polyposis and dysgammaglobulinemia have been reported.[7,8] One author speculates that specific immunologic abnormalities may be responsible for infection by oncogenic viruses.[7] At present, additional case reports and research are necessary before any possible relationships can be established.

Conclusion

Lymphoid polyposis of the gastrointestinal tract is of importance to the surgeon because it can produce symptoms which require surgical intervention. It may also present as a polypoid disorder requiring differentiation from familial polyposis and Gardner's Syndrome. Rarely, lymphoid polyps may occur simultaneously with familial polyposis or Gardner's Syndrome. Histologic confirmation of the diagnosis of lymphoid polyposis is essential before the appropriate therapy can be provided.

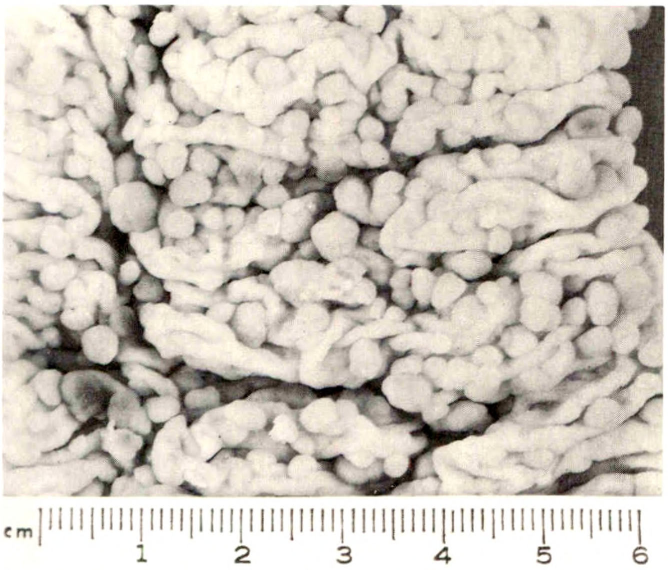

Fig. 3. Closeup photograph illustrating myriads of small adenomatous colonic polyps.

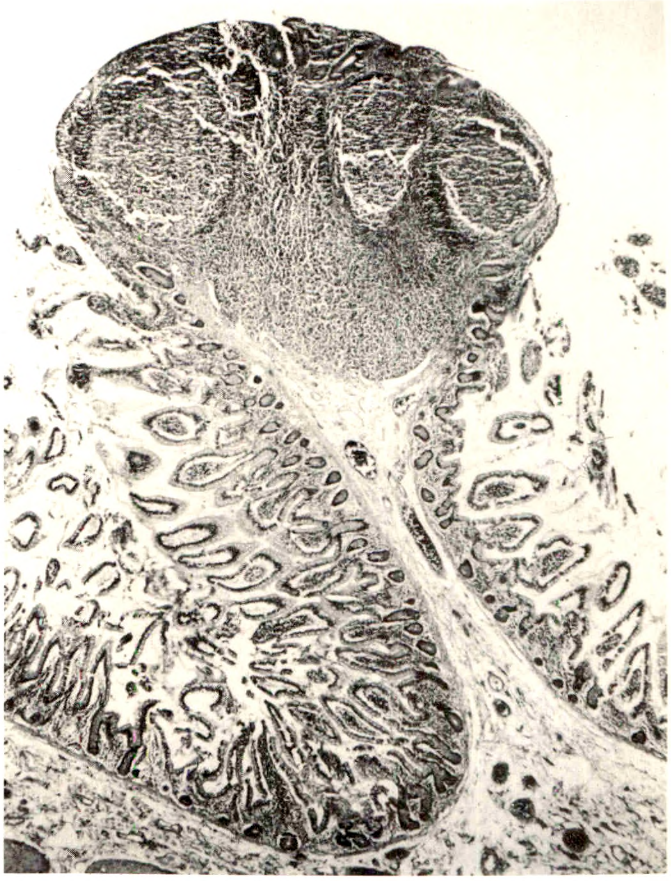

Fig. 4. Microscopic photograph of lymphoid polyp in the colon (×10).

Acknowledgments

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Gastrocutaneous Fistula Following Radiation Therapy for Seminoma of the Testis

ARDEN L. HOTHEM, M.D., JAMES F. NEWSOME, M.D.

A case presentation of a gastrocutaneous fistula following orthovoltage radiotherapy for prophylactic lymph node sterilization for seminoma of the testis is recorded. Many factors determine the response of an organ to radiation and with certain circumstances irreversible damage ensues. The pathologic effects of radiation on the stomach in the reported patient illustrates two stages of injury, acute and chronic. The insidious course of chronic injury eventually destroyed gastric and abdominal wall tissue to create a gastrocutaneous fistula 45 months after radiotherapy. Radiation therapy is a critical therapeutic modality in the treatment of neoplastic diseases and should be carefully administered with close followup of patients for acute and latent radiation effects.

From the Department of Surgery, North Carolina Memorial Hospital, Chapel Hill, North Carolina

RADIOTHERAPY IS A USEFUL METHOD of treating many neoplasms, especially the seminomatous forms of testicular tumors. However, both normal and abnormal tissue can be adversely affected. That gastric ulcers can result from radiation of normal rabbit stomachs was demonstrated by Engelsted in 1938[4] and in normal canine stomachs by Hueper, de Carvajal-Foero in 1944.[7] Numerous reports from investigators including Feiring and Jampol,[5] Bowers and Brick,[1] Elliott and Jenkinson,[3] and Hamilton[6] have documented radiation induced gastric ulcerations and subsequent perforations in humans. It is believed that a gastrocutaneous fistula following radiotherapy for seminoma of the testis has not previously been reported in the American medical literature.

Case Report

M.M., a 32-year-old male was referred to the North Carolina Memorial Hospital for evaluation of a gastrocutaneous fistula in October, 1970. On January 19, 1967 he underwent a left radical orchiectomy (amputation of the spermatic cord at the internal inguinal ring) for pure seminoma. Postoperatively, the para-aortic nodes from the level of the diaphragm to the umbilicus were treated through paired, paralleled, opposing fields measuring 10 × 20 cm with 3,000 r (air dose) to each field over 4 weeks (completed 2-23-67). The iliac nodes were treated in similar fashion through portals measuring 15 × 18 cm with 2,600 r (air dose) to each field over 7 weeks (completed 3-24-67). These doses were calculated to deliver a tumor dose of 3,000 r. The physical factors employed were 250 KV, 1.4 mm of copper half value layer; with an output of 57 r/minute.

During therapy he experienced mild epigastric pain, nausea and some vomiting which were controlled with medication. The epigastric pain and nausea persisted, and 3 weeks after the completion of radiotherapy an upper gastrointestinal x-ray evaluation revealed a gastric ulcer on the anterior wall (Fig. 1a). Despite medical therapy the ulcer progressed over the next 42 months (Figs. 1b–c) until there was complete penetration of the anterior abdominal wall (Fig. 1d) with a draining gastrocutaneous fistula.

Physical examination revealed a well developed and well nourished man complaining of severe burning pain about the site of a draining fistulous stoma 2 cm in diameter in the upper epigastric irradiated area to the left of the midline with gastric mucosa clearly visible in the depths (Fig. 2). The previously described radiation fields were clearly delineated over the abdomen and back as areas of skin with a tough leathery texture, increased pigmentation and telangiectasia. The left testical was surgically absent; there was no palpable lymphadenopathy. The remainder of the physical examination was unrevealing.

Laboratory studies including urinalysis, hemogram, coagulation parameters, electrolytes, blood urea nitrogen, creatinine, glucose, liver function tests, calcium, phosphorus, amylase and uric acid values were within normal limits. The results of radiographic studies including chest film, intravenous pyelogram, selective celiac and superior mesenteric arteriograms and liver scan were also normal.

Two gastric secretory studies were done and the results were within normal limits. In April, 1967 at another hospital, an augmented analysis with histamine was performed and the reported

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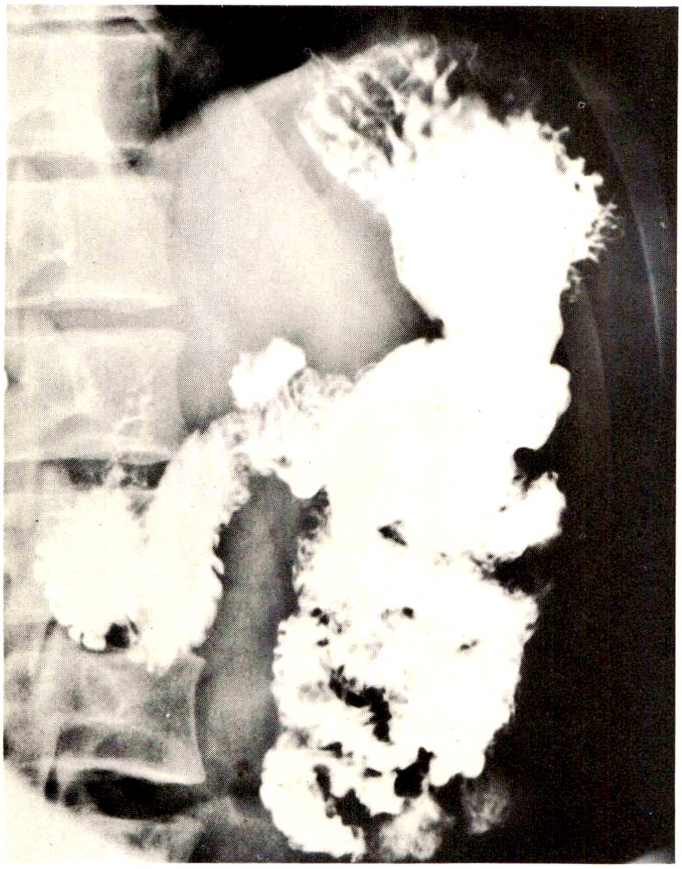

FIG. 1a. Large gastric ulcer on the anterior wall of the antrum.

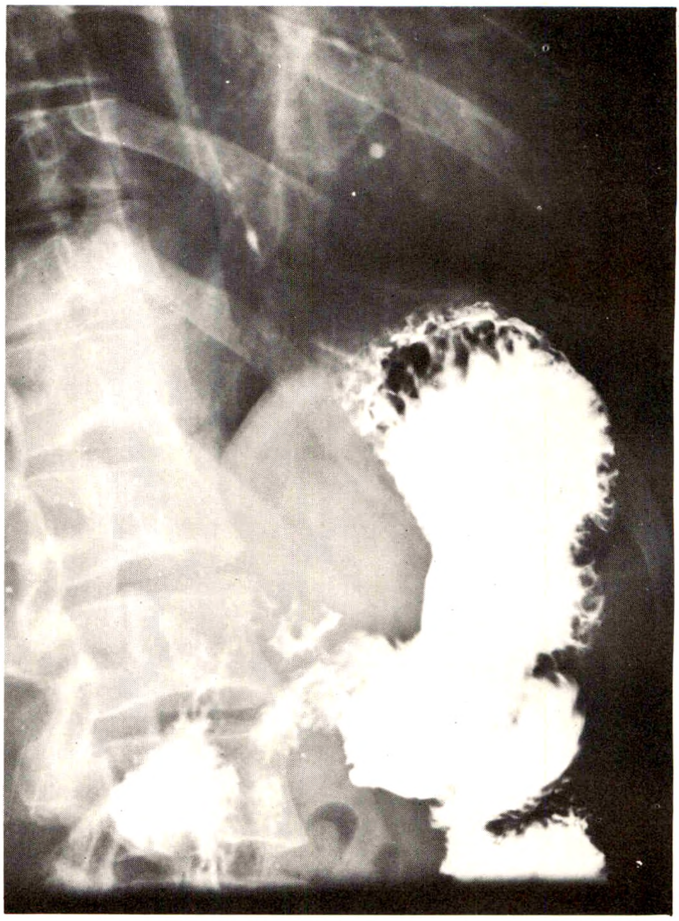

FIG. 1b. Approximately 7 weeks after the initial diagnosis of gastric ulcer was documented the lesion continues to enlarge.

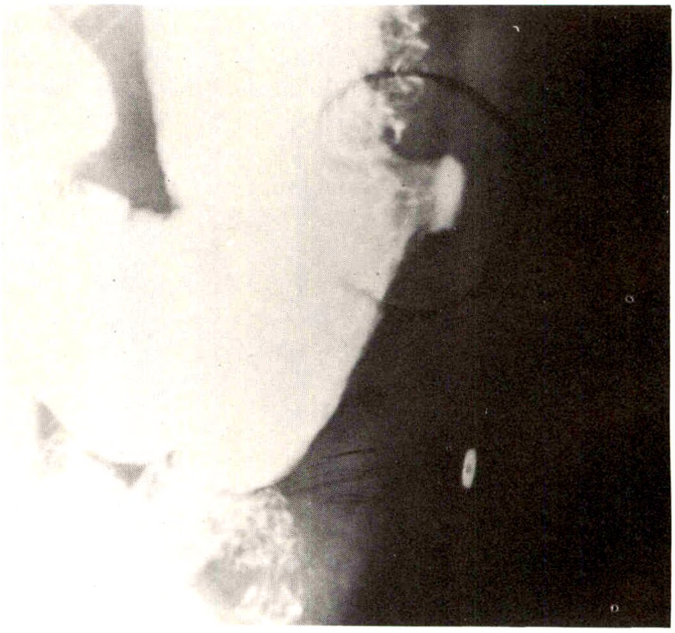

FIG. 1c. The ulceration continues to penetrate the stomach wall despite persistent medical Therapy.

results were a normal amount of free total gastric hydrochloric acid with no free acid upon histamine stimulation. In October, 1970 the basal acid output was 2.393 m Eq/hour; a maximum acid output was not completed because the patient refused to have another histamine injection.

At operation on October 27, 1970 the only significant findings were adhesions of the stomach to the anterior abdominal wall (Fig. 3a) around the site of the fistula; the left lobe of the liver appeared fibrotic. The omentum (Fig. 3b), duodenum and gallbladder were grossly normal in appearance. Surgical treatment consisted of excision of a portion of the irradiated abdominal wall including the gastrocutaneous fistula (Figs. 4 a & b), a distal hemigastrectomy, gastroduodenostomy and primary closure of the abdominal wound.

After surgery, the patient did well and was discharged on a regular diet on the 9th postoperative day. An upper gastrointestinal x-ray evaluation demonstrated a functioning postoperative hemigastrectomy and Billroth I anastomosis (Fig. 5). For the past 36 months he has been free of pain, gainfully employed and without evidence of metastasis.

Discussion

Many factors determine the response of an organ to radiation. The clinical symptomatology and radiation pathology are usually dose dependent.[9] Other aspects such as technical considerations include: total dose, overall treatment time, number of fractions, individual dose, treatment volume, beam quality, field size and quality of

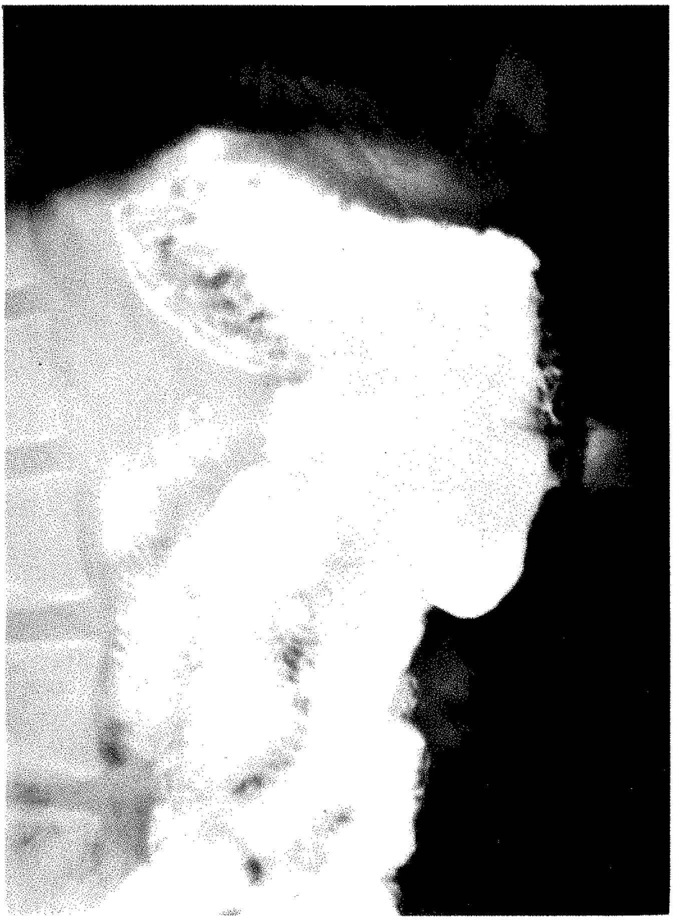

FIG. 1d. The gastric ulcer has continued to errode the stomach and abdominal walls until perforation and creation of a gastrocutaneous fistula results.

technique.[8] The biologic concerns would include: the tumor type, stage of disease, anatomic factors, age, nutritional status, presence of other systemic diseases and hematologic status. A large total dose and especially high daily fractions appear to carry a greater risk of gastric injury than the total irradiated volume.[8]

Nearly all tumors treated in the abdomen demand a therapeutic dose perilously close to the tolerance limits of the vital abdominal organs.[8] Acute ulcers from radiation have been reported at doses as low as 4,300 r/5 weeks[11] and 4,600 r/5 weeks.[13] In Hamilton's series, 50% of the patients receiving 5,000 r (tumor dose) or more, developed epigastric pain. All of his patients who developed gastric ulcers received more than 5,000 r (tumor dose).[6] The accepted tumor dose for prophylactic treatment for pure seminoma is 3,000 r via opposing fields.[2] This tumor dose of radiation was delivered to the reported patient however utilizing orthovoltage equipment required a calculated skin dose of 4,560 r.

The pathologic effects of radiation on the stomach in this patient illustrate the two stages of injury, acute and chronic. The acute phase occured during the treatment and was manifested by transient symptoms of nausea, vomiting, and abdominal pain. Pathologically, the acute stages of radiation injury are characterized by edema, hyperemia and acute inflammation of the gastric mu-

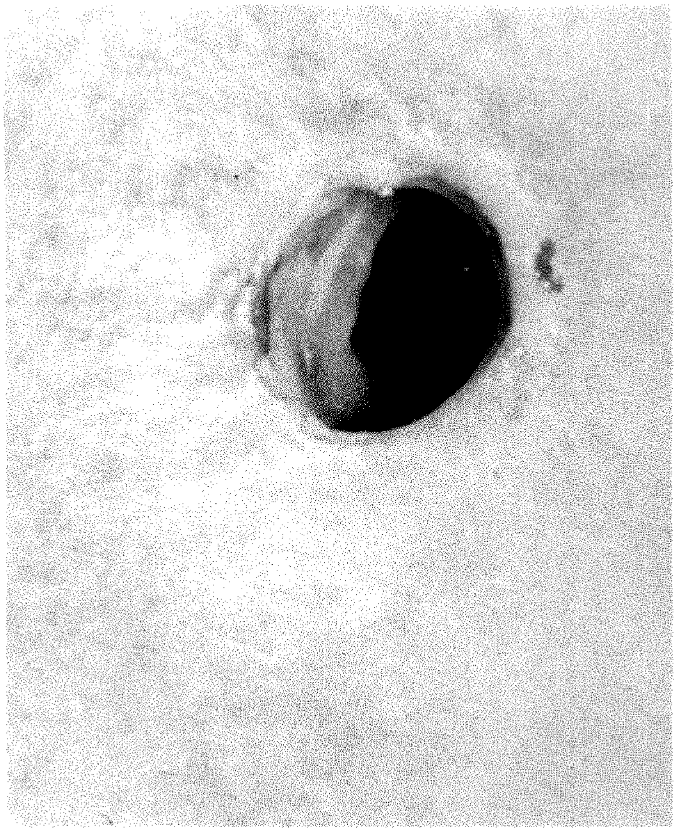

FIG. 2. Gastrocutaneous fistula with gastric mucosa visible in the depths and surrounding radiation dermatitis.

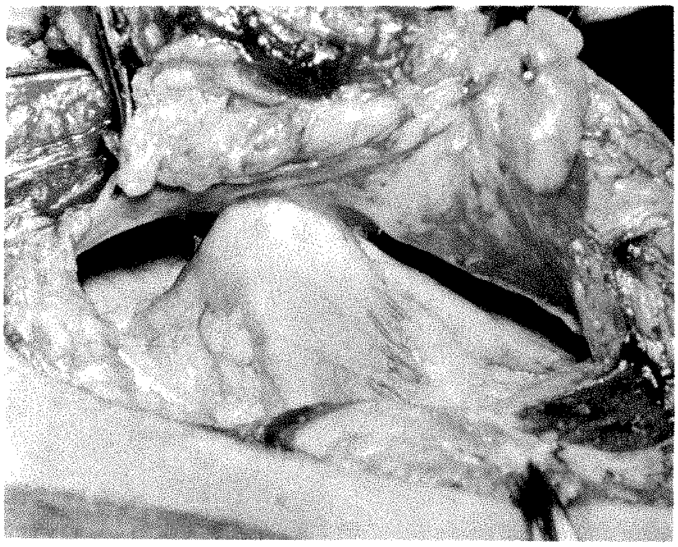

FIG. 3a. View of the adhesion between the anterior stomach and the abdominal wall containing the gastrocutaneous fistula.

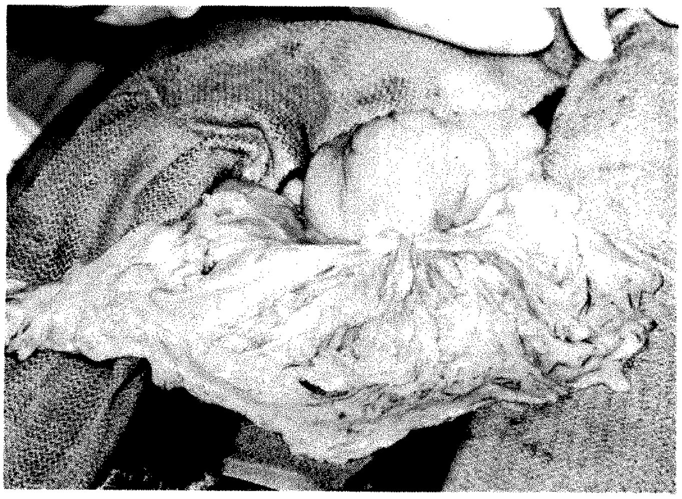

FIG. 3b. The omentum appears grossly normal.

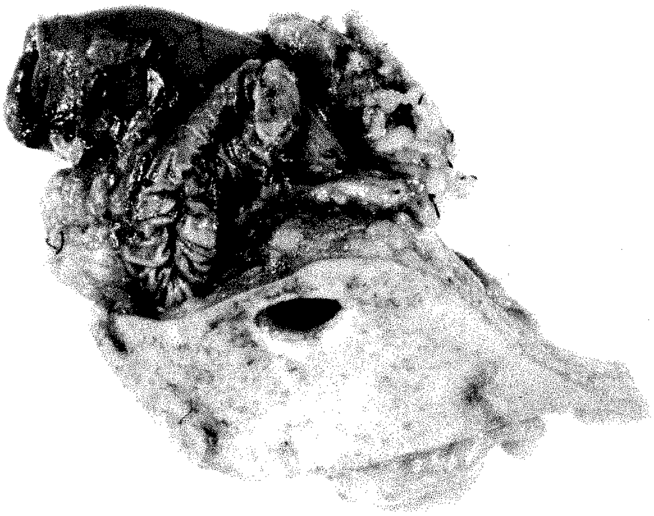

FIG. 4a. The en bloc excision of the gastrocutaneous fistula.

cosa.[10] Inhibition of mitotic activity and death of cells as they enter the next mitosis are common features of radiation damage.[12] Thus delayed epithelial regeneration results in areas of necrosis and edema which can be readily traumatized by ingested food leading to superficial ulceration. This acute phase may be completely reversible with healing by primary intention and normal cellular growth with typical regeneration.

However, primary intention healing did not occur and at some point the irreversible chronic stage began and clinically was characterized by persistent and sometimes severe abdominal pain. The histopathology as explained by Warren and Friedman includes three primary changes in radiation injury of long duration: hyalinization of connective tissue, abnormal fibrosis and hyalinization of

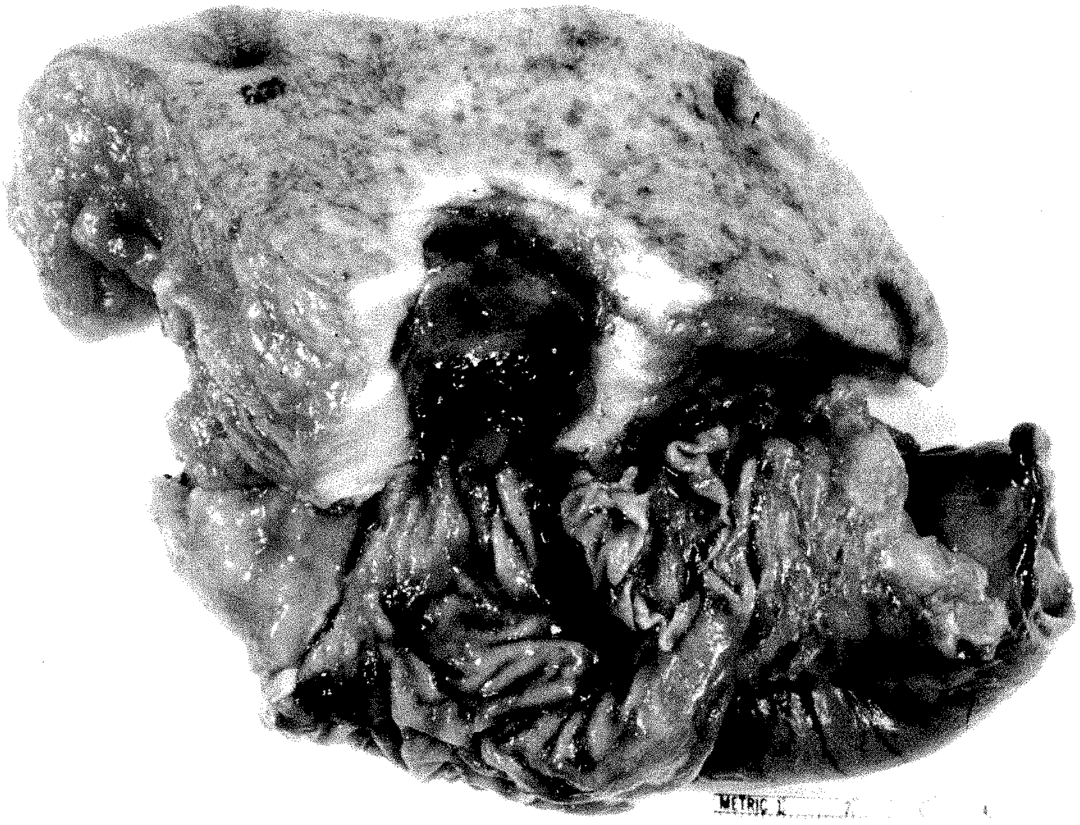

FIG. 4b. The fistula has been opened and demonstrates the fibrosis surrounding the fistula.

blood vessels.[14] (Figs. 6 & 7) With the progression of fibroatrophy of the stomach wall, the gastric motility is impaired with spasm and narrowing in the antrum as well as decreased gastric capacity.[4] The vascular changes are characterized by thickening of the small arteries with stenosis.[3] The subsequent ischemia of the involved gastric tissue would compromise the nutritional state of the mucosal epithelium. Womack has shown that this process is paramount in the production of gastric ulcers primarily because of the relatively sparse capillary perfusion of the mucosa in the region of the pylorus.[15] This suggested mechanism is reinforced by the observation that the radiation induced gastric ulcers reported by Hamilton were all located in the prepyloric antrum of the stomach.[6]

It is assumed that these described changes from radiation which lead initially to superficial ulceration may continue and cause penetration of the underlying damaged tissue. In this patient who received a large amount of cutaneous radiation to the epigastrium the intractible process of ulceration and perforation was abetted by the vascular and connective tissue damage to the stomach and abdominal wall. The persistent destruction of this compromised tissue produced complete mural penetration of the stomach and, through adhesions between the stomach and abdominal wall, a gastrocutaneous fistula.

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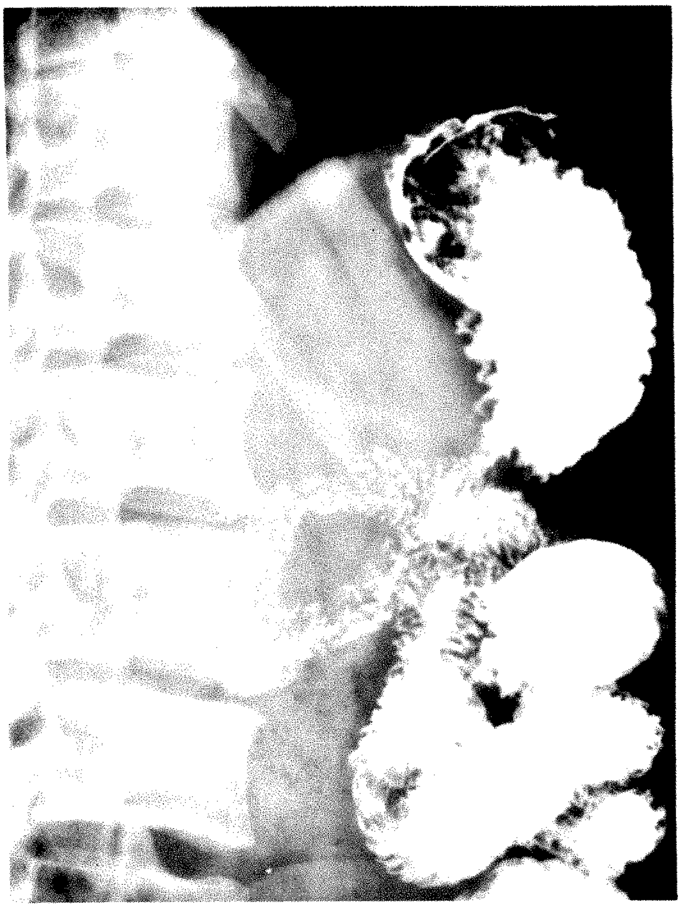

FIG. 5. The postoperative Billroth I anastomosis is intact and functioning.

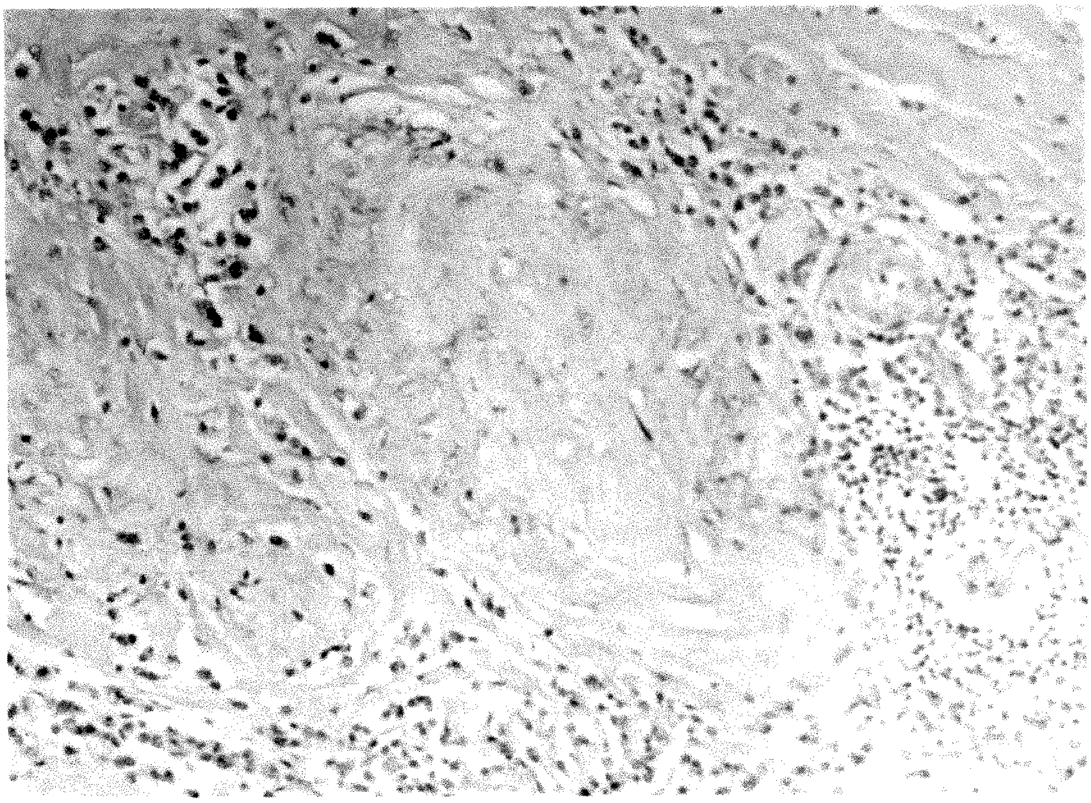

FIG. 6. A section through the abdominal wall which was radiated. Note the intense fibroblastic activity and the altered fibroblast morphology with plump nuclei and large amounts of amphophilic cytoplasm. Centrally located one can see an obliterated artery with chronic perivascular inflammation. (H and E, × 400)

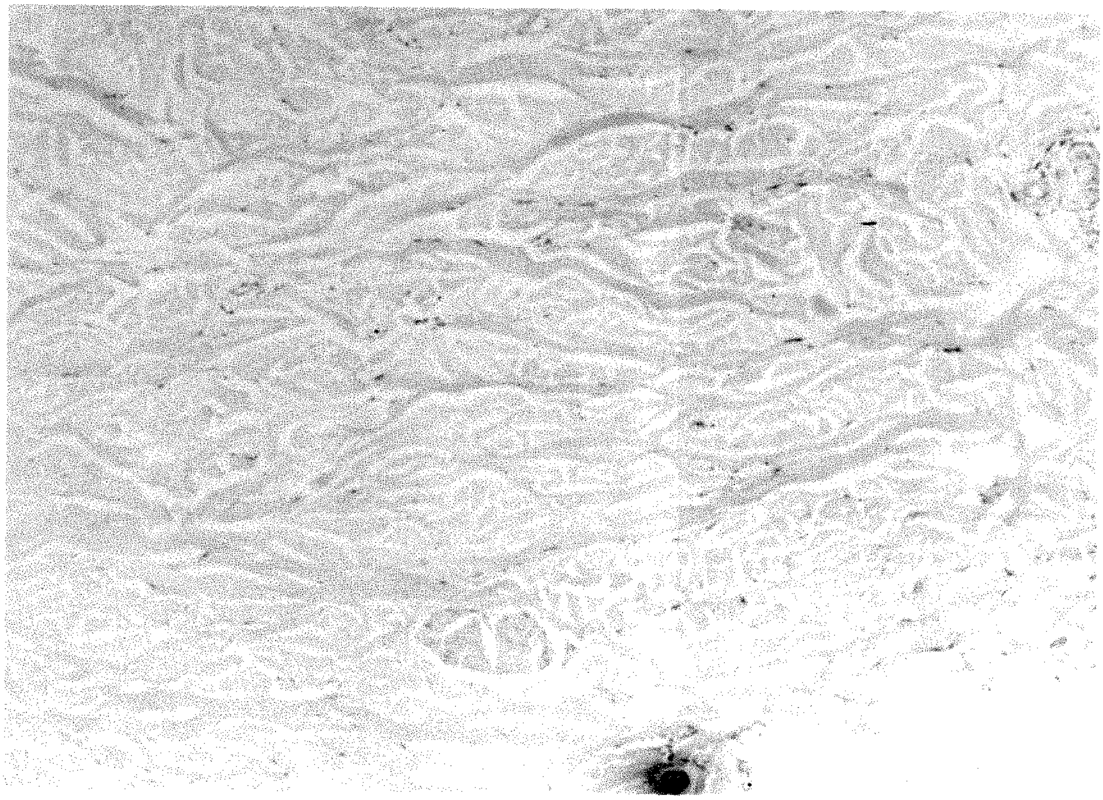

FIG. 7. Muscular atrophy with interlacing collagenous septa in the irradiated abdominal wall (H and E, ×200).

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Healing of the Canine Aorta After Endarterectomy:

A Scanning Electron Microscopy Study

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Endarterectomy sections of canine aorta were examined in various stages of healing by scanning electron microscopy. In all specimens the endarterectomy site was quickly covered by a thin fibrin-platelet coagulum with varying amounts of thrombus. Neoendothelization began before one week and was virtually completed by one month except on areas of heavy thrombus deposition. While this study does not prove the origin of the neoendothelial cell, it suggests that neoendothelial cells are derived from pre-existing endothelium and advance over the endarterectomy site from the junction zone of the normal aorta and to a lesser extent from the orifices of branching vessels.

MUCH OF OUR KNOWLEDGE concerning vascular wound healing has been obtained from studies of prosthetic grafts. Relatively little attention has been directed towards the basic healing of large arterial injuries such as that produced by endarterectomy. Healing after vascular injury is known to begin with the deposition of varying amounts of thrombus at the site of injury. The thrombus is organized and heals as "neointima," and in man may undergo fatty degeneration, ultimately becoming indistinguishable from atheromatous lesions.[2,14]

There is considerable controversy over the origin of the neoendothelial cell and even its mechanism of coverage. The present study was designed to explore the mechanisms of surface healing of normal vessels after endarterectomy and possible origins of the endothelial cell using the scanning electron microscope.

Materials and Methods

Eleven anesthetized dogs weighing 25–35 kg were subjected to a 3 cm or greater endarterectomy of the abdominal aorta between the renal arteries and the trifurcation. Atraumatic technique was used and the adventitia was not dissected from the aorta to minimize damage to the vasa vasora. A single injection of 1000 units of heparin was given prior to cross-clamping the aorta. An endarterectomy plane was developed in the outer third of the tunica media and the arteriotomy was closed with a running 6-0 braided Dacron cardiovascular suture.

The animals were sacrificed with a lethal dose of heparinized barbiturate at 3 hours, 7, 14, 21, 28 and 90 days postoperatively. Specimens were carefully removed, examined for gross thrombus, and fixed in either 10% formalin or 3% glutaraldehyde buffered to pH 7.4 with 0.1 M sodium cacadylate for periods of no less than 24 hours.

Following fixation, representative sections from areas with heavy and minimal thrombus as well as adjacent normal aorta were selected for scanning electron microscopy. These specimens were progressively dehydrated in a graded series of ethanol and then in an increasing ratio of Freon to ethanol. The samples were dried in a Bomar Critical Point Dryer at 40 C and under 900 lb/in^2 pressure with a gas escape rate of 50 lbs per 30 seconds to prevent ice crystal artifacts commonly seen

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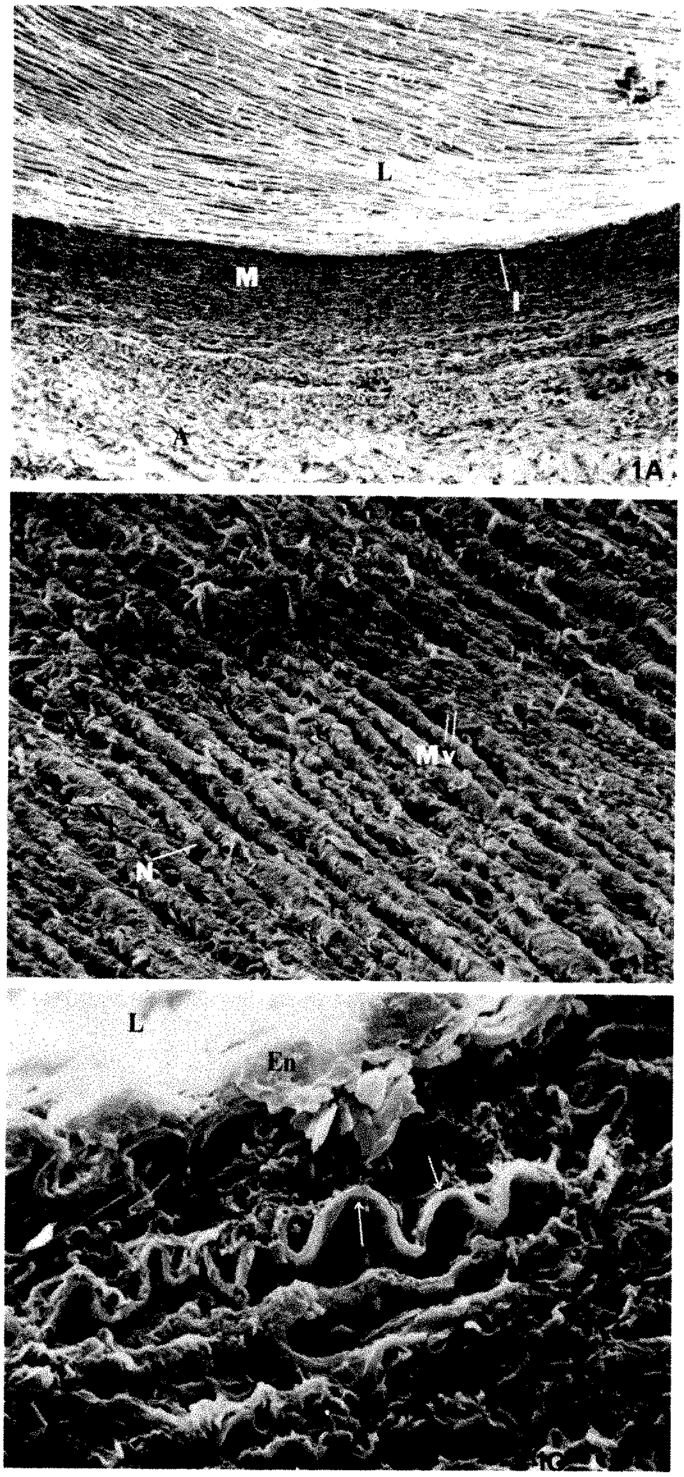

FIG. 1. Normal canine abdominal aorta. 1a. (Top) Normal aorta showing endothelium and longitudinal section. Corrugations run ongitudinally with scattered fibrin deposition. (L—Luminal Surace; I—Intima; M—Media; A—Adventitia) 44 ×. 1b. (Center) Higher power view of normal endothelium. Cell nuclei and pleomorphic microvilli are present. (N—Nucleus; Mv—microvilli) 75 ×. 1c. (Bottom) Cross section of normal aorta showing inernal elastic lamina (arrows). (L—Luminal Surface; En—Endohelium) 962 ×.

with the freeze drying techniques. After coating the samples in a vacuum chamber with a layer of evaporated gold-palladium alloy to produce electro-conductivity, they were examined with a Cambridge Stereoscan S4 scanning electron microscope.

Results

Normal Aorta

The normal abdominal aorta in non-endarterectomized dogs is far from smooth. There are longitudinally oriented corrugations evident on normal aortas that appear to run in a gentle spiral (Figs. 1a, b). On cross section (Fig. 1c) the corrugations only roughly correspond to undulations of the internal elastic lamina. Specimens fixed with the aorta distended show a flattening of the corrugations which never completely disappear. Endothelial cells appear as large elongated cells with centrally placed nuclei. The cells are oriented in the longitudinal axis of the vessel. Numerous evaginations, which have been previously described as nutritional microvilli that may also direct plasma flow, can be seen projecting from the endothelial surface.[13,16]

Three Hours

Three hours after endarterectomy, the specimen is grossly free of thrombus except in the ostia of the ligated vessels and in some areas along the endarterectomy junction zone (Fig. 2a). However, fibrin deposition is already occurring over the entire endarterectomy site (Fig. 2b).

Seven Days

One week after endarterectomy, early re-endothelization is occurring in places with minimal thrombus near the endarterectomy junction zone. No re-endothelization was found in the center of the endarterectomized segments. Areas of moderate to heavy thrombus formation are still undergoing organization and appear as a carpet of platelet-fibrin coagulum over the endarterectomy site. (Figs. 3a, b). Figure 3c is a longitudinal section as seen by light microscopy showing the endarterectomy through the media with no evidence of thrombus.

Fourteen Days

Two weeks after endarterectomy, re-endothelization is evident over wide areas except on those with heavy thrombus. The bare areas of the initial fibrin coagulum appear to be virtually organized with neoendothelial cells beginning to proliferate over the surface (Fig. 4a). Figure 4b shows a slight misalignment of a suture line. Examination of this surface at higher magnification reveals a vasa vasorum with neoendothelium advancing

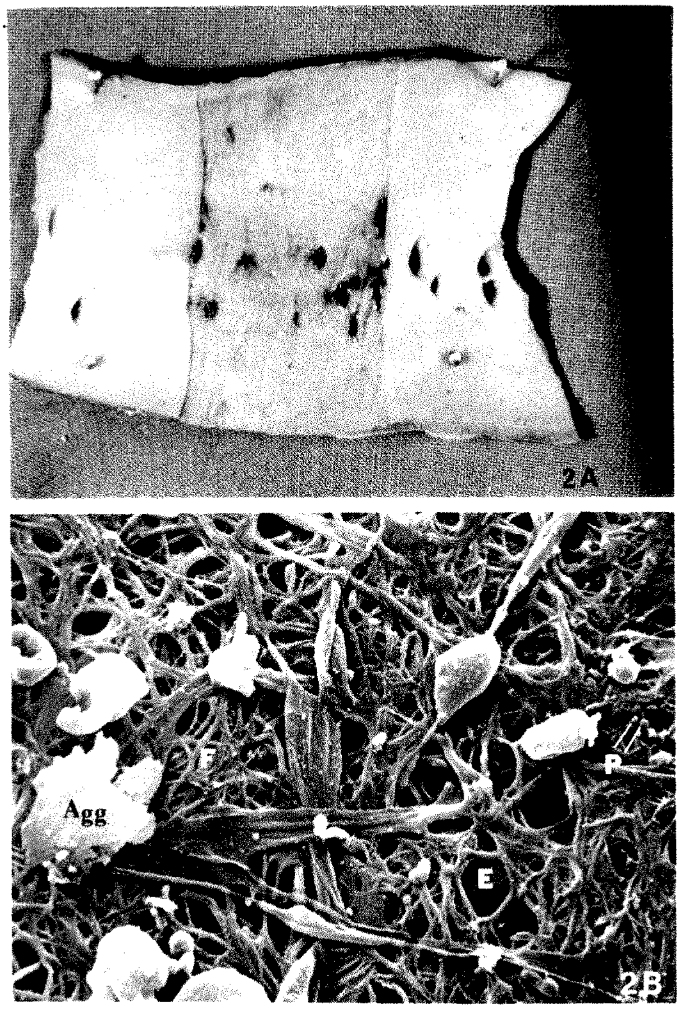

FIG. 2. Three hours post endarterectomy. 2a. (Top) Gross specimen showing site of endarterectomy and early thrombus deposition at the junction zone and in the orifices of ligated lumbar arteries. 2b. (Bottom) Early fibrin deposition on a grossly bare area of endarterectomy site of Fig. 2A. Segments of an elastic lamina are deep to the fibrin mesh. (F—Fibrin; P—Platelet; Agg—Platelet-Leukocyte Aggregate; E—Elastic Lamina) 4,375 ×.

outward to cover the vertical surface of the exposed tunica media (Fig. 4c).

Twenty-one Days

Healing is virtually complete by three weeks except in the center of the endarterectomy section. An advancing front of neoendothelium is evident, which extends from both junction zones toward the center of the endarterectomized segment (Fig. 5a). In other sections, linear groups of cells appear separated by uncovered areas (Fig. 5b). Neoendothelial cells can be seen emerging from ostia of small vessels with varying degrees of coverage (Figs. 5c, d).

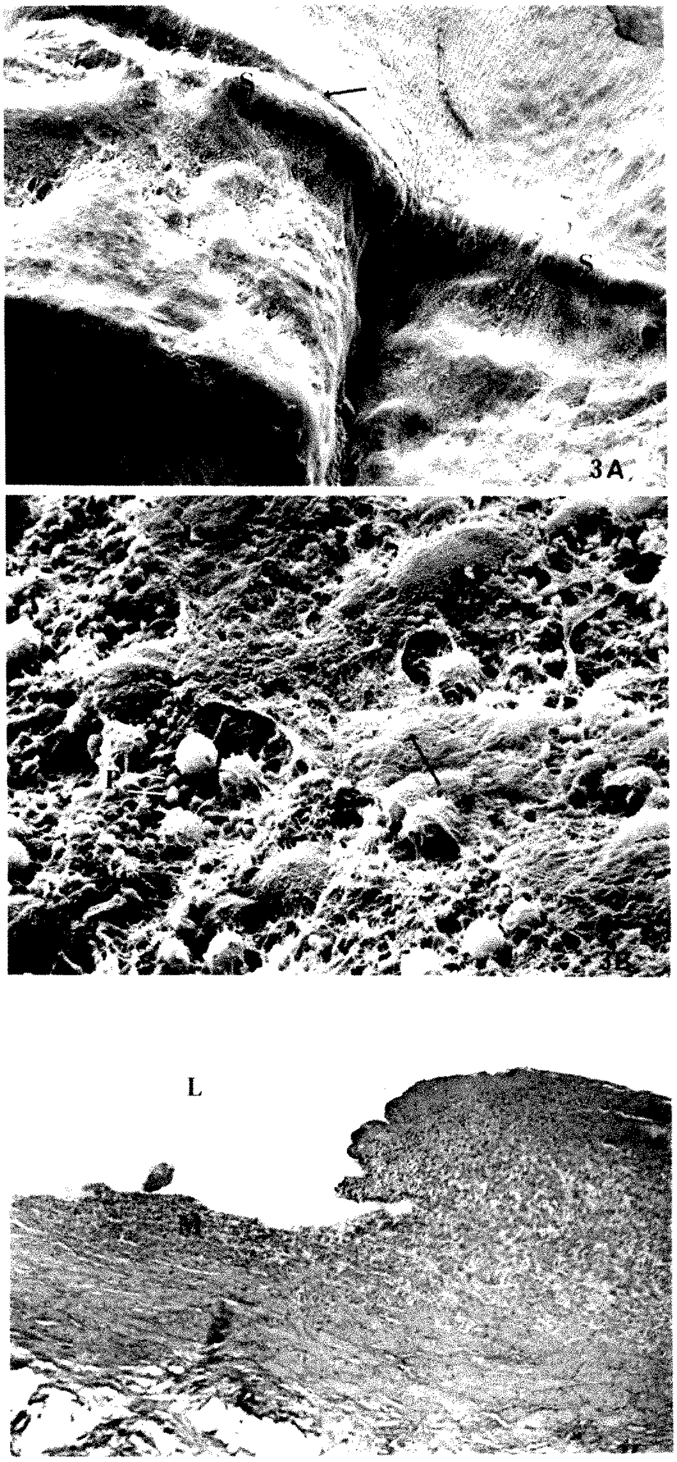

FIG. 3. Seven days post endarterectomy. 3a. (Top) Low power view of one week endarterectomy showing slight thrombus deposition at the junction zone (arrow). The rounded structure is a thrombus coated suture(s). The groove is the arteriotomy (17 ×). 3b. (Center) Typical area of heavy thrombus with a platelet-fibrin coagulum beginning to coat cells in thrombus (arrow). (P—Platelets) 1,312 ×. 3c. (Bottom) Longitudinal section of endarterectomy junction demonstrating cleavage plane in tunica media. (L—Lumen; M—Tunica Media). 56 ×.

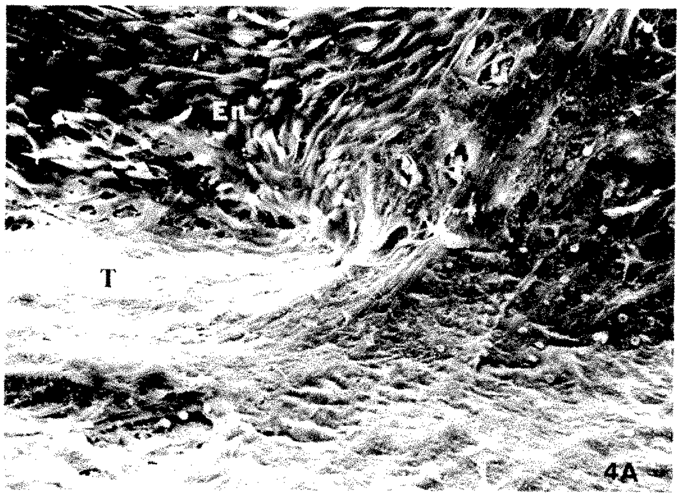

FIG. 4a. Fourteen days post endarterectomy. Two weeks after endarterectomy no endothelial cells are evident on a thin layer of thrombus. There is beginning neoendothelization of the bare area. (T—Thrombus; En—endothelium) 175 ×.

Twenty-eight Days

By one month all specimens were healed except on a few areas of heavy thrombus deposition. The cells in many areas have "bright" and cobblestone appearance while in other areas are flattening and appearing to mature (Figs. 6a, b). As the neoendothelial cells flatten, they tend to become oriented to the longitudinal axis of the vessel.

Ninety Days

Three months post endarterectomy, healing and maturation is complete (Fig. 7a). Figure 7b shows a suture across the arteriotomy site. In the healed sections, corrugations present on normal aorta do no re-form. Shallow corrugations are at first glance present but can be easily seen running in all directions creating a pattern much like a coarse weave. In light microscopy specimens there is no evidence of regeneration of elastic fibers in the endarterectomized media.

Discussion

The scanning electron microscope which allows much greater resolving power than the light microscope and a depth of field comparable to the human eye is an invaluable tool with which to study a surface phenomenon such as endothelial healing.

In normal arteries, corrugations are evident by light microscopy but are more easily seen by scanning electron microscopy. Corrugations in dogs appear to run as long longitudinal spirals similar to rifling in gun barrels. It was observed that even in fixed distended specimens, corrugations were still evident. The function of corrugations at this point is only speculative but it would appear that they may be effective in directing flow of a non-Newtonian fluid by lessening turbulence.

The vasa vasorum play an important function in ar-

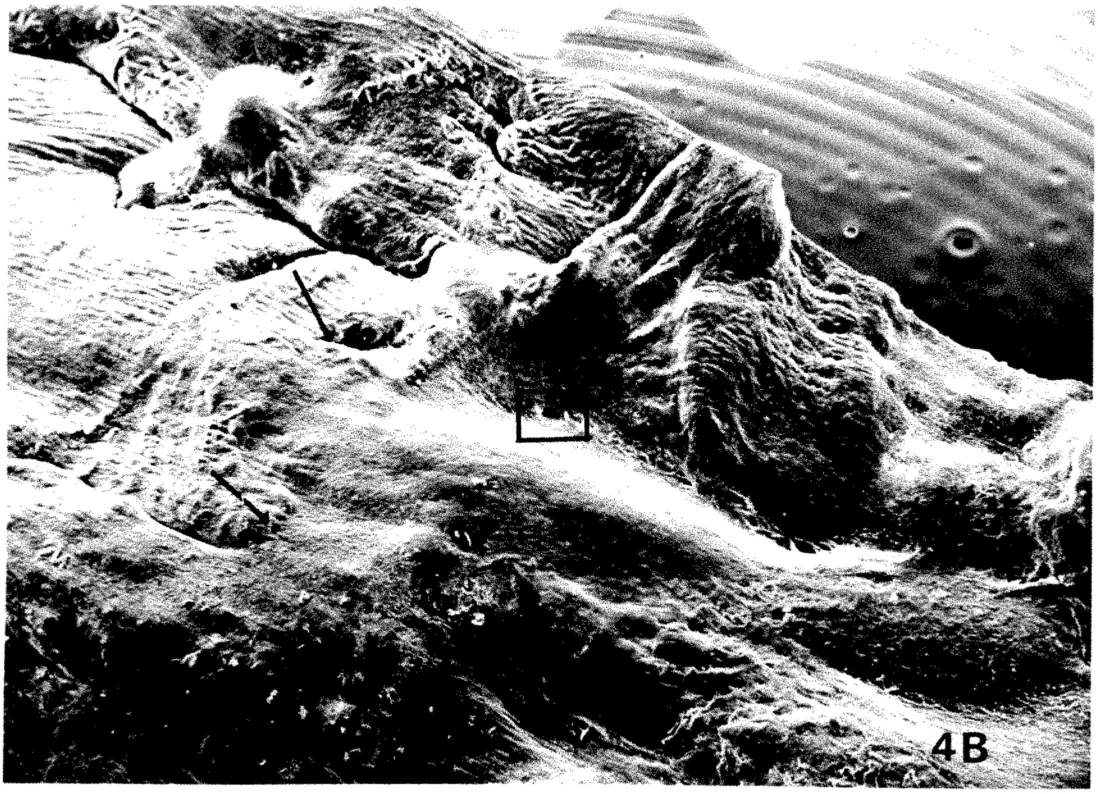

FIG. 4b. Fourteen days post endarterectomy. Slight misalignment of a arteriotomy. Most of the endarterectomy devoid of thrombus appears healed. (Arrows—Junction zone; V—Vasa vasora) 30 ×.

terial wound healing. In elastic and larger muscular arteries luminal diffusion provides nutrition to only the inner 500–600 μ while the remainder of the vessel is supplied by the vasa.[1] If intimal thickening develops gradually, the vasa may be able to increase distribution, but if sudden thickening of the intima occurs as with thrombus deposition, ischemic changes occur which may explain the poor healing seen in human vascular prostheses. Duguid[2] published a classical paper in 1948 describing mural thrombi as a cause of intimal thickening in autopsied human aortas of all ages. He felt these events were continuously occuring, often undergoing fatty degeneration, and subsequently becoming histologically identical to atherosclerosis. Duguid's hypothesis was later experimentally proven in hypothyroid, hyperlipemic dogs subjected to endarterectomy.[6,11]

Following endarterectomy, healing begins with deposition of a thin platelet-fibrin carpet over the entire en-

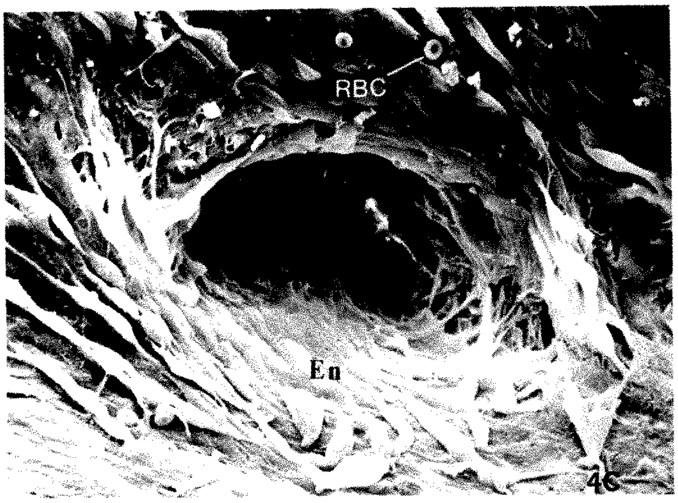

FIG. 4c. Fourteen days post endarterectomy. Higher power of 4b showing vasa vasora with neoendothelium extending from the orifice. (RBC—Red Blood Cell; En—Endothelium) 750 ×.

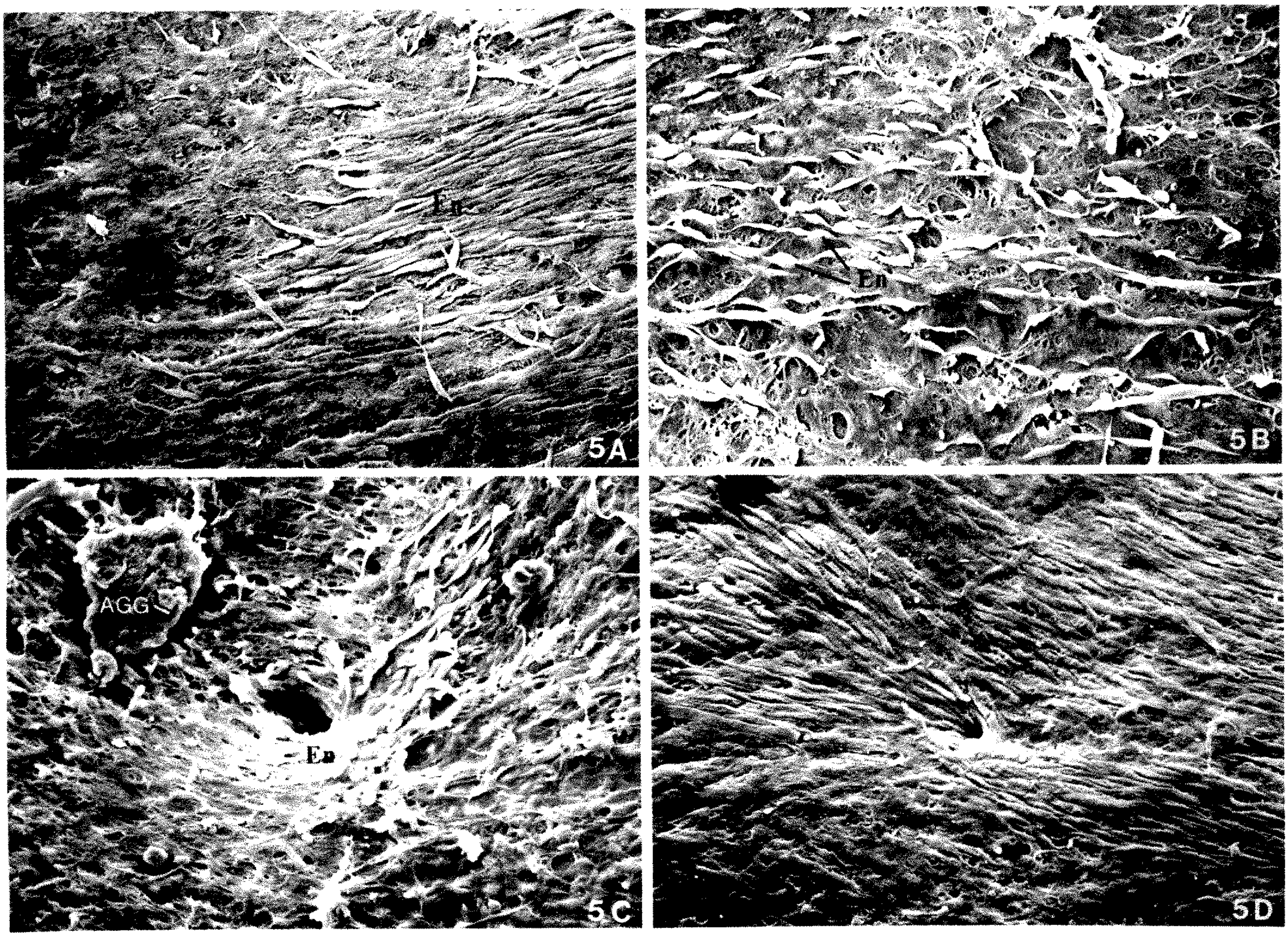

FIG. 5. Twenty-one days post endarterectomy. 5a. Advancing front of neoendothelium (En). 198 ×. 5b. Early re-endothelization. Most cells are longitudinally oriented in strands but isolated cells in various positions are present. 198 ×. 5c. Early migration of neoendothelium from a small branch vessel. (En—Endothelium; Agg—Platelet-Leukocyte Aggregate) 198 ×. 5d. Orifice of small branch vessel with more advanced coverage and beginning maturation of endothelium. 198 ×.

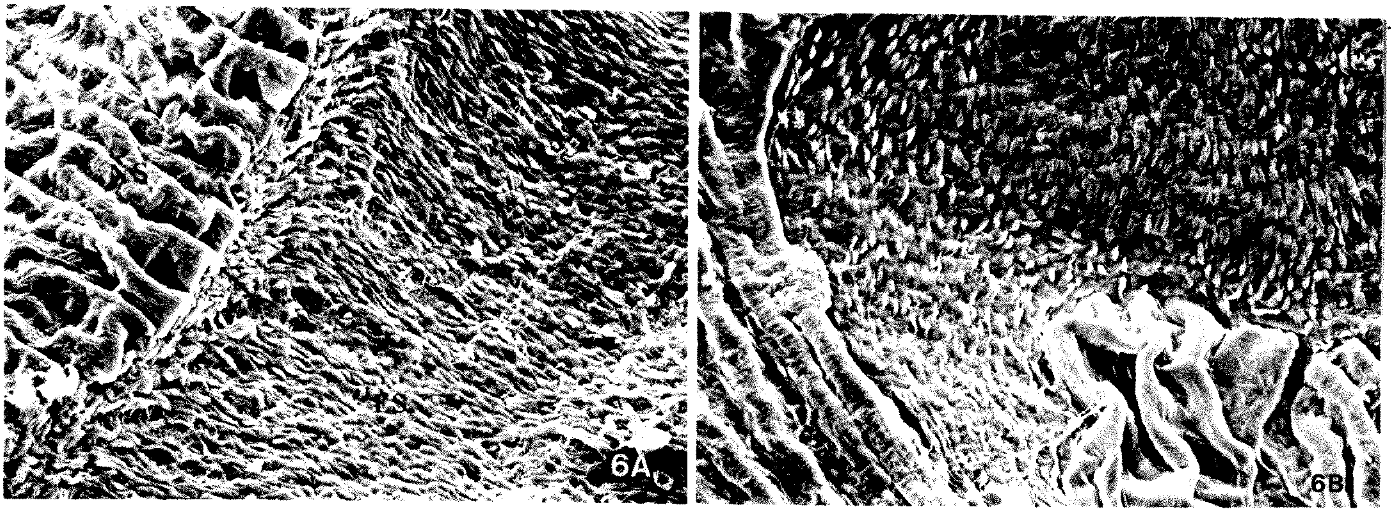

FIG. 6. Twenty-eight days post endarterectomy. 6a. (Left) The junction zone (arrow) by one month is well healed but has continuing cell proliferation. (NS—Normal Surface; ES—Endarterectomy Surface). 175 ×. 6b. (Right) Similar section to 6A but neoendothelial cells are flattened suggesting maturation (175 ×).

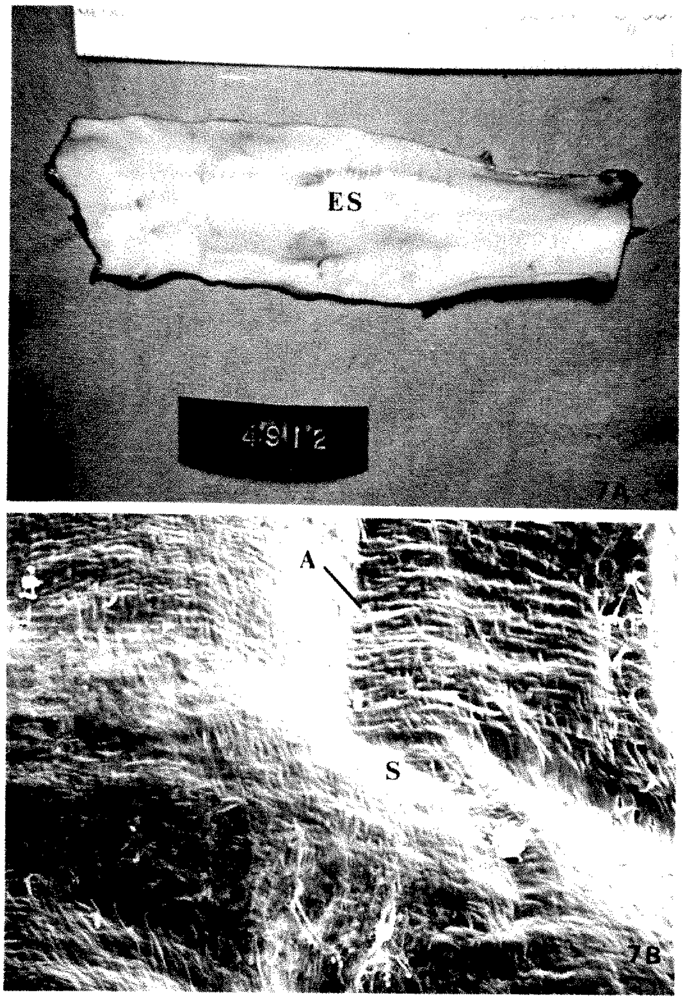

FIG. 7. Ninety days post endarterectomy. 7a. (Top) Gross specinen with a well healed glistening neoendothelial surface and suure line. (ES—Endarterectomy Surface). 7b. (Bottom) Scanning iew of 7A showing re-endothelization of the midportion of the ndarterectomy segment. (A—Arteriotomy; S—Suture) 130 ×.

darterectomy site with rough or uneven areas filling with varying amounts of thrombus. This surface quickly becomes anti-thrombogenic with no further thrombus deposition evident. By one week, re-endothelization is well under way and is virtually complete by one month. However, even at three months, areas of heavy thrombus are still not covered by neoendothelium, suggesting that such areas may never heal. This correlates with Sabiston's[11] observation in hypercholesterolemic dogs that atheromatous changes in vessels prior to endarterectomy tend to directly influence the degree of postoperative luminal narrowing and that in time mural thrombi can be a nidus for atheromatous changes.[6]

The neoendothelial cell resembles normal endothelium in that it is a large spindle-shaped cell with a centrally placed nuclei. However, neoendothelial cells are first seen at the junction zones and at the ostia of branch vessels. As neoendothelial cells migrate from the junction zone towards the center of the endarterectomy site, the cells often appear randomly oriented but in time tend to become longitudinally oriented which Flaherty *et al.*[3] suggested was an effect of sheer force and pressure stress.

Because neoendothelization starts adjacent to normal intima, this study suggests, but does not prove, that neoendothelium is derived from preexisting endothelium. There are currently four commonly accepted theories of its origin. One of the earliest theories suggests that neoendothelium is derived from a blood bourne precursor and represents layering out of monocytes or fibroblasts.[5,7,12]

Re-endothelization in many vascular prosthetic studies has been interpreted to occur as an advancing sheet from normal intima or from the ostia of vessels.[4,9,10] On several specimens endothelium could be seen coming from the ostia of branch vessels and in one case from a vasa vasorum.

Endothelium is friable and cells frequently slough. Cells resembling endothelium have been isolated from circulating blood and grown in tissue culture. It has been suggested that circulating endothelial cells may be deposited upon damaged surfaces and proliferate from these points.[7] Random islands of neoendothelium were noted on an occasional specimen in which the ostia of a vessel could not be located. This could suggest that these cells were deposited from the blood stream, or more likely, intervening areas of neoendothelium sloughed since all of the islands were adjacent to other areas of neoendothelium.

The most recent theory suggests that neoendothelium is derived from smooth muscle cells which have migrated from the tunica media into the thrombus at the site of injury. These same smooth muscle cells were formerly considered to be fibroblasts, but on transmission electron microscopy fulfill the histological criteria for smooth muscle.[8,15] If the neoendothelial cell is derived from smooth muscle and migrates to the intimal surface of the aorta, we would have expected to see uniform healing across the entire length of the endarterectomy segment. Healing in all specimens occurred as an extension from normal endothelium with migration toward the center of the endarterectomized segment. In no instance were cells resembling endothelium seen emerging from the fibrin lattice.

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The Advantages of ^{131}I-orthoiodohippurate Scintiphotography in the Management of Patients After Renal Transplantation

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Renal scintiphotography with ^{131}I-hippurate was the primary diagnostic procedure in evaluating renal failure and complications in over 500 transplant patients. This diagnostic test has become our principal method of evaluation and followup of renal transplants, especially in the early post-transplant period. It has accurately distinguished tubular necrosis, rejection, and other complications in the post-transplant period. Its simplicity, safety and accuracy are of great value to transplant surgeons and their patients.

AFTER KIDNEY TRANSPLANTATION, the status of the graft must be periodically assessed to diagnose and treat renal failure and other complications. Since 1967, more than 500 renal transplants have been performed at the University of California Medical Center, San Francisco. During this period, renal scintiphotography with excretion of ^{131}I-orthoiodohippurate was the principal method used to evaluate the graft and to complement clinical impressions and chemical determinations. This report describes our experience with more than 1500 scintiphotographic studies in renal transplant patients and is the largest series to be reported.

Materials and Methods

Approximately 100 microcuries of ^{131}I-orthoiodohippurate (OIH) were injected into the adult patient and serial four-minute exposure photographs were obtained for 36 minutes. Occasional late followup scintiphotographs were taken, if necessary, after intervals of one to 24 hours. The amount of isotope that accumulated in the kidney and urinary bladder (or urine container) was also estimated.

The OIH scintiphotographic study was performed on the first postoperative day in 320 patients with cadaver grafts, providing early assessment of the graft, and serving as a baseline for subsequent studies when indicated. Because of the excellent earlier functional status of grafts from live related donors, baseline studies were not routinely performed in this group of recipients. Instead, a change in the clinical course of the graft was used as the indication for OIH scintiphotography.

Direct scintiphotography of blood flow distribution in the grafts was carried out with ^{99m}Tc-DTPA (technetium-99m diethyl-tetramine-penta-acetic acid) as a supplemental examination in selected instances of suspected vascular compromise.

Results

Table 1 lists the clinical situations in which renal scintiphotography has proved useful and reliable in our renal transplantation experience.

Immediate Post-transplant Evaluation

Renal scintiphotography is useful in the immediate post-transplant period as a baseline for future comparative studies, and to evaluate the success of the vascular and ureteral anastomoses. Good tracer uptake in the entire renal cortex indicates adequate perfusion, while nor-

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TABLE 1. *Indications for Renal Scintiphotography*

1. Immediate Post-Transplant Evaluation
2. Acute Rejection
3. Acute Tubular Necrosis
4. Acute Rejection Superimposed on Acute Tubular Necrosis
5. Urinary Extravasation
6. Ureteral Obstruction
7. Renal Artery Occlusion
8. Iliac Vein Thrombosis with Renal Vein Obstruction
9. Segmental Renal Lesions (Regional Ischemia)
10. End-Stage Chronic Rejection

mal drainage of urine confirms patency of the ureteral anastomoses. Figure 1 shows a cadaver kidney with excellent function, confirmed by maximum radioisotope labeling of the renal cortex within the first four minutes of the study and followed by excellent clearing of the radiopharmaceutical from the renal cortex in the subsequent photographs. In the early postoperative period, indwelling Foley catheters are inserted in our patients, necessitating evaluation of the isotope count in the urine container for an accurate appraisal of renal excretory function. When renal scintiphotographic studies are performed after the Foley catheter is removed, the proximity of the bladder to the kidney in the transplant patient permits evaluation of the radiopharmaceutical content in the kidney and bladder on the same scintiphotographs. A transplant with excellent function will ordinarily show 6,000 (6K) to 10,000 (10K) counts per minute in the urine container at 36 minutes post-injection of 100 microcuries of OIH, and the counts in the half of the camera field of view containing the kidney will be approaching background count rates at 36 minutes. Any deviation from the normal scintiphotographic study encompasses a wide differential diagnosis of conditions encountered in renal transplantation, as described below.

Acute Rejection

Acute rejection of the graft was the main reason for performing OIH scintiphotography. Acute rejection requires prompt diagnosis and differentiation from other etiological mechanisms of renal failure, so that appropriate corrective therapy may be instituted. It is crucial, however, that a baseline OIH scintiphotographic study be obtained on the first postoperative day. In acute rejection, comparison with the original scintiphotographs will show: 1) reduced rate of uptake of OIH; 2) frequent irregular uptake of OIH in the graft cortex; 3) delay in intrarenal transit of OIH; and 4) decreased excretion of tracer into renal collecting structures. Figure 2 demonstrates good initial graft function followed by acute rejection and subsequent recovery. During a severe rejection episode, renal uptake of OIH may at times be almost negligible. The continued uptake of tracer by the graft, even though minimal, has been used as our primary criterion for continuing treatment of acute rejection episode. If failure of isotope uptake is demonstrated, rejection therapy is terminated and transplant nephrectomy is performed. The diagnosis of irreversible rejection can be readily made if serial scintiphotographic studies are performed at two to three day intervals in patients with severe rejection crises. A pre-injection scintiphotograph must be obtained in order to evaluate residual isotope from the previous studies.

Acute Tubular Necrosis

Although renal failure secondary to acute tubular necrosis occurred in less than 20% of the recipients of cadaver grafts, tubular necrosis is the most common cause of immediate post-transplant failure of graft function. Figure 3 illustrates expected similar behavior of the two kidneys obtained from a cadaver donor with prolonged severe hypotension. Despite expected tubular necrosis in some cadaver donor transplants, it is important to document this diagnosis and exclude an hyperacute rejection, cortical necrosis, or vascular obstruction as an associated mechanism in early post-transplant renal failure. We routinely follow the status of the kidney with acute tubular necrosis by performing serial OIH scintiphotos. In this manner, acute rejection superimposed on acute tubular necrosis may be detected.

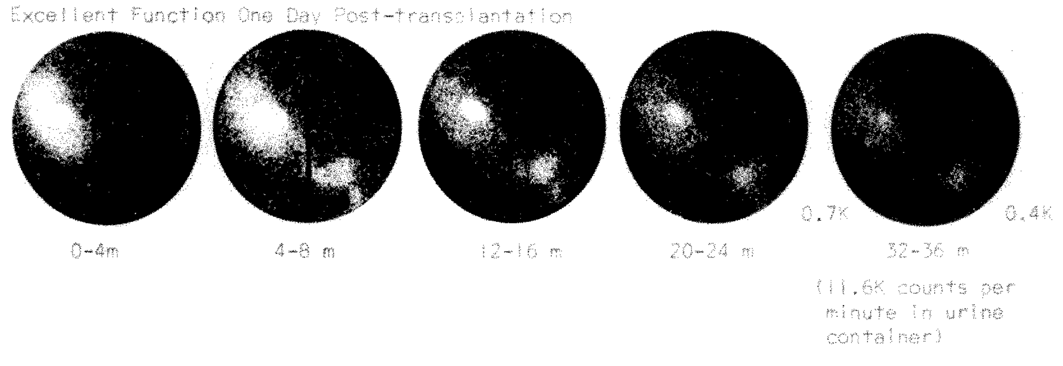
Excellent Function One Day Post-transplantation
0-4m
4-8 m
12-16 m
20-24 m
0.7K
0.4K
32-36 m
(11.6K counts per minute in urine container)

FIG. 1. Cadaver kidney with normal function one day post-transplantation. The bladder is drained by a catheter, and therefore accumulation of the tracer is in the urine container and not in the bladder.

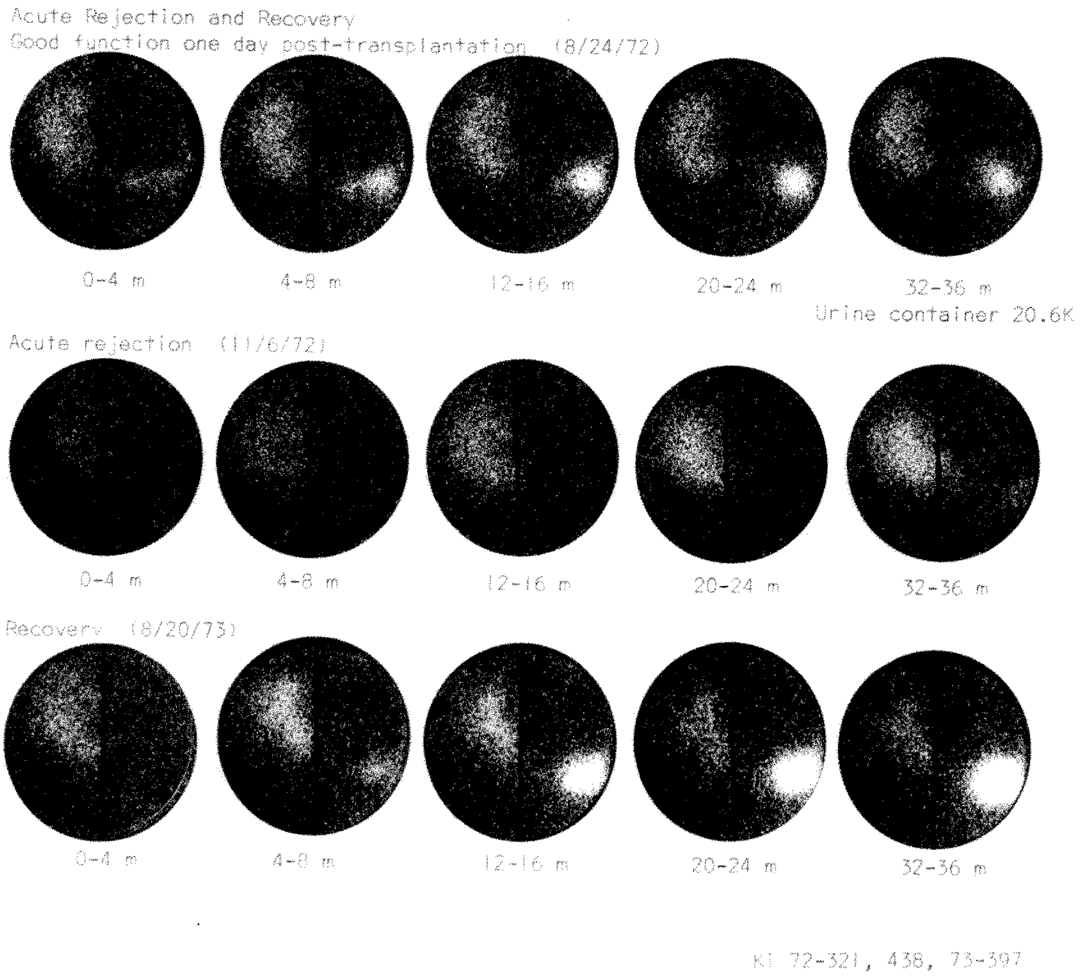

FIG. 2. A series of renal scintiphotographic studies showing good initial graft function, followed by acute rejection and subsequent recovery.

Acute Rejection Superimposed on Acute Tubular Necrosis

Diagnosis of transplant rejection in the presence of acute tubular necrosis is a major diagnostic problem. The usual signs of acute rejection, such as a rising creatinine, decreased urinary output, weight gain, and possible urinary sediment and chemical changes are negated because of the usual severe oliguria accompanying the acute tubular necrosis. In our experience, serial evaluation of patients with continuing uncomplicated acute tubular necrosis has shown no change in uptake in the concentration of ^{131}I-hippuran by the graft. Fever and graft tenderness or failure of improvement of graft function, are indications for scintiphotographic evaluation of the graft. Comparative evaluation of serial OIH scintiphotographic studies is a reliable method to detect rejection superimposed on acute tubular necrosis. Deterioration of uptake of the radiopharmaceutical and reduced excretion, compared to the baseline study 24 hours post-transplantation is diagnostic of rejection. Figure 4 is an example of acute tubular necrosis, superimposed acute rejection and graft recovery following rejection therapy.

Urinary Extravasation

Renal scintiphotography has been useful in establishing the diagnosis in two patients with ureteral urinary extravasation and in one patient with urinary extravasation from the renal pelvis. In none of these patients was there evidence of urinary drainage from the abdominal wound, nor was the correct diagnosis considered before the performance of renal scintiphotography. Figure 5 demonstrates the ureteral leak that occurred eight months following transplantation.

Ureteral Obstruction

There are varying degrees of ureteral obstruction and renal scintiphotography has been helpful in diagnosis except in patients with mild ureteral obstruction. Severe ureteral obstruction with oliguria or anuria can be differentiated from other causes of renal failure by the presence of a large hilar defect in the graft corresponding to absence of radioisotope in an enlarged renal pelvis. In a patient with slowly rising creatinine, moderate ureteral obstruction could be differentiated from rejection by the accumulation and persistence of radioisotope in an

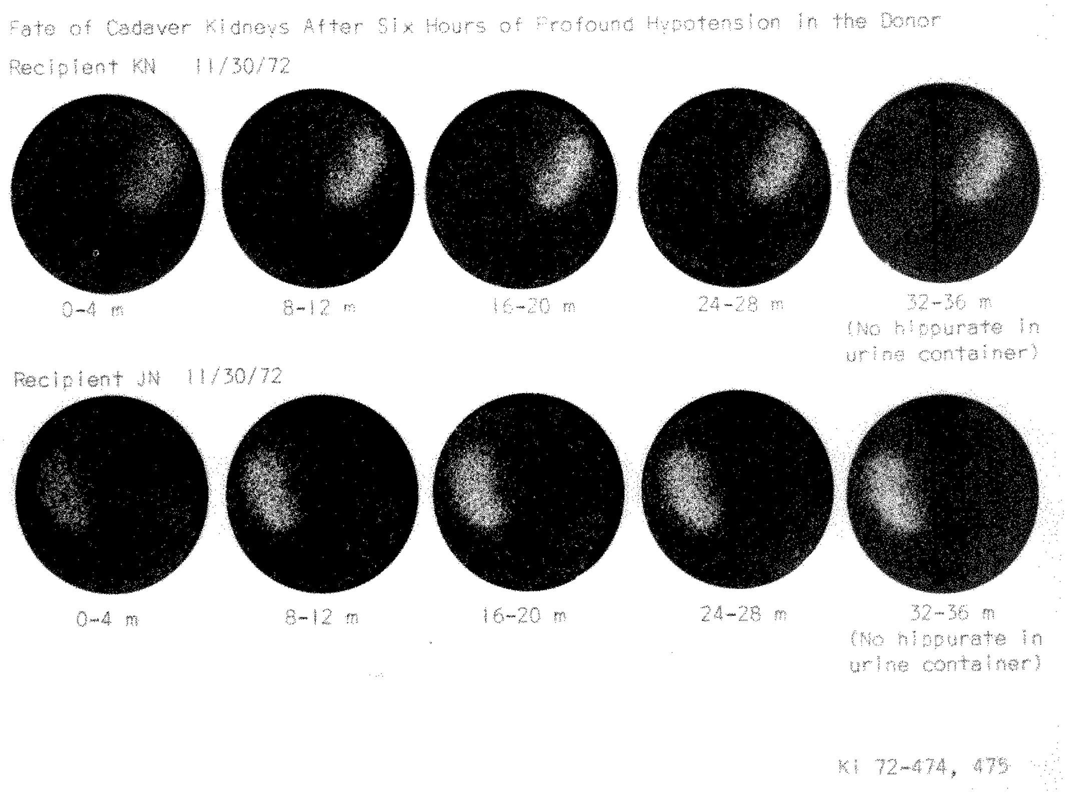
Fate of Cadaver Kidneys After Six Hours of Profound Hypotension in the Donor
Recipient KN 11/30/72
0-4 m
8-12 m
16-20 m
24-28 m
32-36 m
(No hippurate in urine container)
Recipient JN 11/30/72
0-4 m
8-12 m
16-20 m
24-28 m
32-36 m
(No hippurate in urine container)
Ki 72-474, 475

FIG. 3. Scintiphotographs of kidneys recovered from cadaver donor with prolonged severe hypotension. Both kidneys have undergone acute tubular necrosis and demonstrate uniformity of tracer uptake without evidence of excretion.

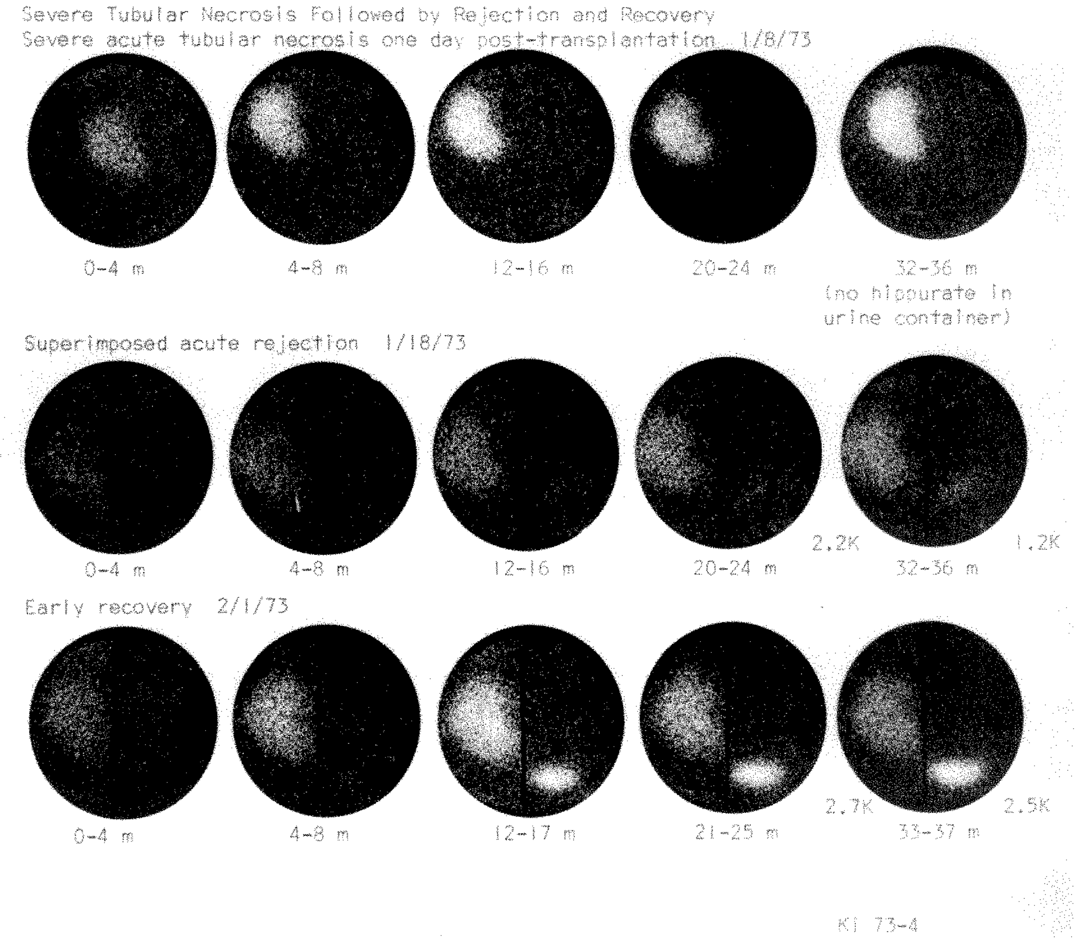
Severe Tubular Necrosis Followed by Rejection and Recovery
Severe acute tubular necrosis one day post-transplantation 1/8/73
0-4 m
4-8 m
12-16 m
20-24 m
32-36 m
(no hippurate in urine container)
Superimposed acute rejection 1/18/73
0-4 m
4-8 m
12-16 m
20-24 m
2.2K
32-36 m
1.2K
Early recovery 2/1/73
0-4 m
4-8 m
12-17 m
21-25 m
2.7K
33-37 m
2.5K
Ki 73-4

FIG. 4. A series of renal scintiphotographic studies of a cadaver kidney with acute tubular necrosis, followed by superimposed acute rejection and subsequent recovery.

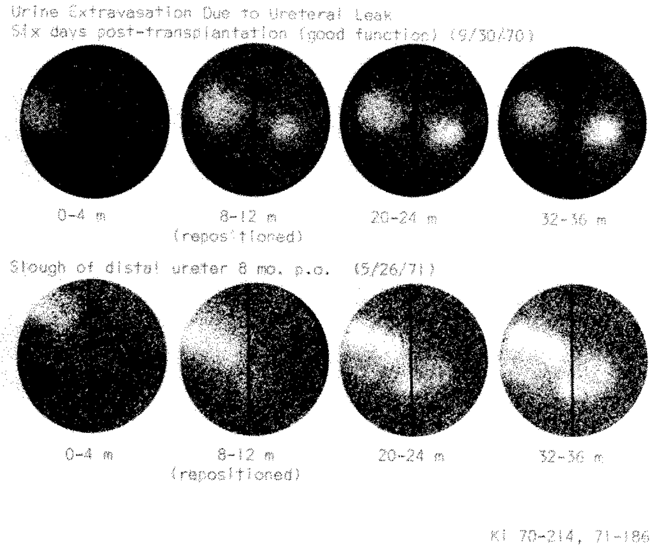
Urine Extravasation Due to Ureteral Leak
Six days post-transplantation (good function) (9/30/70)
0-4 m
8-12 m (repositioned)
20-24 m
32-36 m
Slough of distal ureter 8 mo. p.o. (5/26/71)
0-4 m
8-12 m (repositioned)
20-24 m
32-36 m
KI 70-214, 71-186

FIG. 5. Renal scintiphotographic studies demonstrating early graft function and a spontaneous ureteral leak at eight months post-transplantation.

enlarged renal pelvis (Fig. 6). Anatomical definition of the site of obstruction can best be obtained later by radiographic means. Nevertheless, the diagnosis of moderate ureteral obstruction can be suggested by renal scintiphotography and appropriate therapy instituted.

Renal Artery Occlusion

Acute renal artery occlusion must be considered as part of the differential diagnosis of early post-transplant renal failure. This is particularly true in cadaver grafts if the paired kidney in another recipient has satisfactory function. In contrast to acute tubular necrosis, the graft shows virtually no uptake of the radiopharmaceutical because of lack of renal perfusion. Immediate renal scintiphotography is essential in patients who suddenly develop oliguria or anuria following satisfactory urinary output in the immediate post-transplant period. The entire renal scintiphotographic study need not be carried out, since lack of renal perfusion will be evident after the first several four-minute time frames. Immediate surgical exploration can still result in renal salvage as was accomplished in one case.

Iliac Vein Thrombosis with Renal Vein Obstruction

Three patients in this series had iliac vein thrombosis and secondary renal vein obstruction. This was clinically manifested by deep femoral and iliac vein thromboses on the ipsilateral side, moderate proteinuria, and rapidly deteriorating renal function. Both ^{131}I-hippurate and technetium DPTA scintiphotographic studies had been performed in these patients to document decreased renal perfusion and for serial assessment of the graft during the period of anticoagulation therapy. The OIH scintiphotography consistently provided the most useful information. In all three patients, renal function returned to normal after appropriate therapy with heparin.

Segmental Renal Lesions (Regional Ischemia)

Segmental renal lesions are easily detectable. Segmental renal infarction secondary to a divided upper polar artery at the time of cadaver donor nephrectomy is shown in Fig. 7.

End Stage Chronic Rejection

^{131}I-hippuran renal scintiphotography is useful as an interval study in end-stage chronic rejection, when the patient has been returned to hemodialysis. If uptake of the radioisotope is demonstrated, however minimal, we usually keep the graft *in situ,* hoping to replace it with a suitable cadaver graft during a single operation so that the same iliac vessels can be used after the chronically rejected graft is removed. However, if renal scintiphotography fails to show radioisotope uptake, the graft is removed and retransplantation is performed later if a suitable cadaver graft is not available at the time of transplant nephrectomy.

Discussion

In the transplant patient, the postoperative period can be simple and uneventful or extremely complicated. As far as the transplanted kidney is concerned, differential diagnosis of renal failure can be extremely difficult in two situations. The first is a sudden decrease in urinary output shortly after transplantation and the second is the diagnosis of rejection superimposed upon acute tubular necrosis. In these and other cases, renal scintiphotography has been of inestimable value on our transplant service.

Multiple diagnostic procedures have been used in the past, including arteriography, retrograde pyelography, open biopsy and intravenous pyelography. Although these procedures can be of great help, most of them are uncomfortable for the patient, are difficult to perform repeatedly, and have some morbidity.

In our experience with renal scintophotography in over 500 transplants, serial ^{131}I-hippurate scintiphotographic studies have proved of great value in evaluation of kidney transplant structure, function, and viability. The study causes no discomfort or morbidity to the patient, is simple, and provides a large amount of information at relatively low cost. Additional studies can be performed on the same patient, if they are needed, to evaluate renal function. Furthermore, good renal visualization is possible in uremia, which is not uncommon after transplantation. We have found that this method can adequately distinguish between tubular necrosis and rejection. It

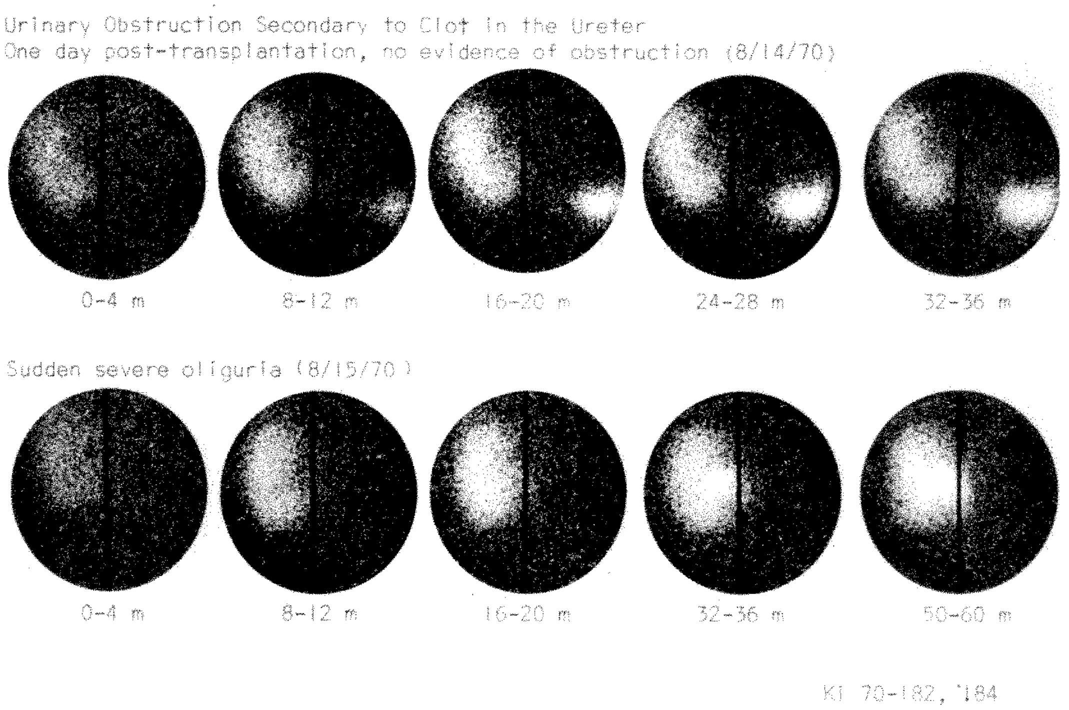
Urinary Obstruction Secondary to Clot in the Ureter
One day post-transplantation, no evidence of obstruction (8/14/70)
0-4 m
8-12 m
16-20 m
24-28 m
32-36 m
Sudden severe oliguria (8/15/70)
0-4 m
8-12 m
16-20 m
32-36 m
50-60 m
Ki 70-182, 184

FIG. 6. This cadaver transplant had good function one day post-operatively, followed by moderately severe ureteral obstruction on the second post-operative day. Moderate accumulation and persistence of radioisotope is seen in an enlarged renal pelvis.

can also diagnose renal artery obstruction and ureteral obstruction.

One particular point should be stressed. The control, or first scintiphotographic scan, should not be done until 24 hours after transplantation. The renal damage produced by anoxia in acute tubular necrosis tends to reach its maximum after 24 hours. Further renal deterioration because of persistent tubular necrosis is not seen after this period. If the scintiphotographic studies are done immediately after operation, then further deterioration may occur over the ensuing 24 hours, due to the initial underlying anoxic damage producing the tubular necro-

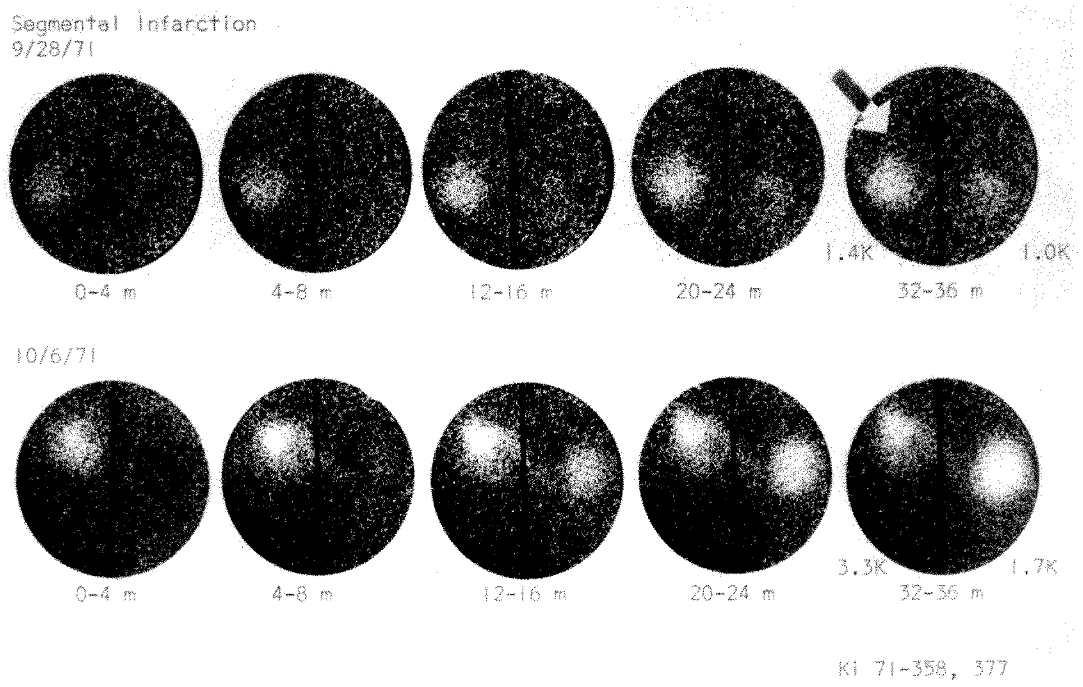

FIG. 7. Renal scintiphotographic studies of cadaver kidney with a divided upper polar artery. There is total absence of uptake of the tracer in the upper pole of the transplanted kidney.

sis. We have found that deterioration in the scintiphotographic studies after 24 hours is due to rejection. The efficacy of anti-rejection treatment in the patient with tubular necrosis can thus be adequately followed by improvement of the scintiphotographic study even though the patient may remain oliguric.

It is also of great advantage to know at what time anti-rejection treatment should be stopped if renal function continues to deteriorate. If the uptake of ^{131}I-hippurate continually decreases on serial scintiphotography, rejection therapy with all its inherent hazards can be stopped and the kidney can be removed at an optimum time.

It should be stressed, however, that the diagnosis of rejection cannot be made on a single renal scintiphotographic study. It is absolutely necessary to have a control study, preferably taken on the first postoperative day, to serve as the baseline for comparison for all future photographs.

As we have indicated, we perform transplant nephrectomy concomitantly with retransplantation whenever possible. Serial renal scintiphotography can be used to follow a patient with a viable but poorly functioning kidney who may have returned to dialysis while awaiting retransplantation. As long as the photographs still show graft viability, the kidney can be left in place and nephrectomy can be performed whenever a second graft becomes available. However, if at any time the scintiphotographic study shows no uptake of the radioisotope, nephrectomy should be performed to prevent complications of graft necrosis.

The choice of the radiopharmaceutical is important. We have found blood flow studies with technetium-99m radiopharmaceuticals to be of little value. For example, in a patient with severe tubular necrosis and very low renal blood flow, the technetium blood flow study is of little help. However, OIH will be accumulated by viable renal cells and ultimate excellent renal visualization is obtained, after an adequate interval for accumulation of the tracer.

Scintiphotography is of limited value in two particular problems. In a hypertensive patient with suspected renal artery stenosis, in the transplant graft, arteriography should be performed for diagnosis. Scintiphotographic diagnosis of renal artery stenosis would depend upon comparison of ischemic cortex function with function of non-ischemic cortex and no opportunity exists for such comparison in the transplant patient. It is also of limited diagnostic value in mild ureteral obstruction in which case intravenous pyelography will be of greater help. However, renal scintiphotography with OIH has at times suggested the possibility of partial ureteral obstruction which was subsequently verified and exactly identified by intravenous pyelography.

Acknowledgments

We wish to acknowledge the contributions of Drs. Shelby Miller and Robert Hattner in the interpretation of these scintiphotographic studies.

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CONCEPT

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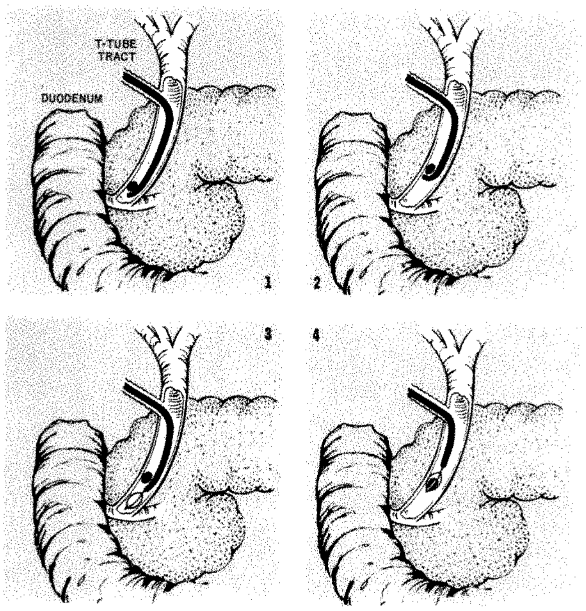
Unique maneuverability of the soft-steerable catheter tip permits the physician to dislodge, manipulate and reposition the stone(s). Contrast media is injected through the Luer-Lock and the Open Lumen of the MEDI-TECH catheter to enhance visualization. Then, with the stone in desired position, a wire basket or snare is passed through the Tuohy-Borst fitting and the open lumen to the site. When the stone is secured, the entire assembly is withdrawn. Although the soft-tip provides sufficient torque for this procedure, patient discomfort is minimal and no anesthesia or pre-medication is used.



*REFERENCE

Burhenne, H. J., Non-operative Retained Biliary Tract Stone Extraction — A New Roentgenologic Technique, AMER. J. ROENTGENOLOGY, Vol. CXVII, No. 2, pp. 388-399, February 1973.

AN X-RAY CINE FILM of the Burhenne procedure is available. Please contact MEDI-TECH to arrange a viewing of the film and to obtain copies of reference articles plus complete information on the MEDI-TECH/BURHENNE Biliary Catheter System.

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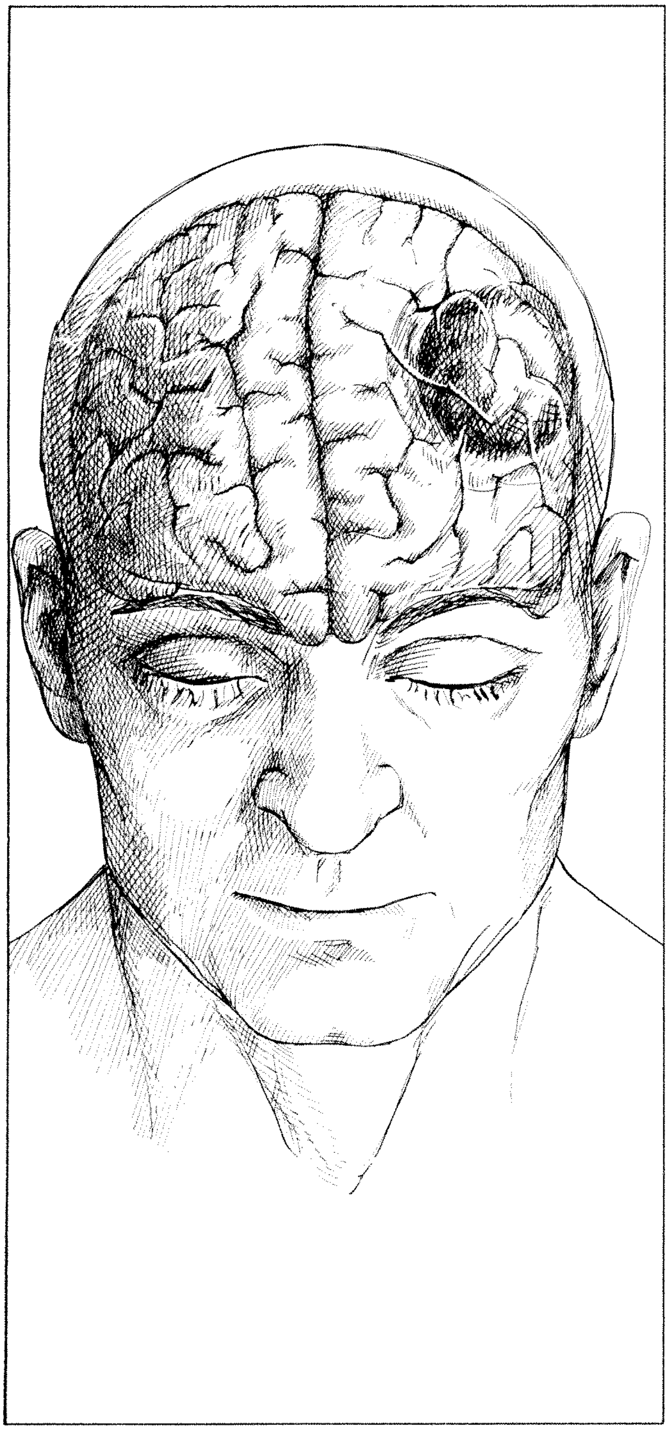
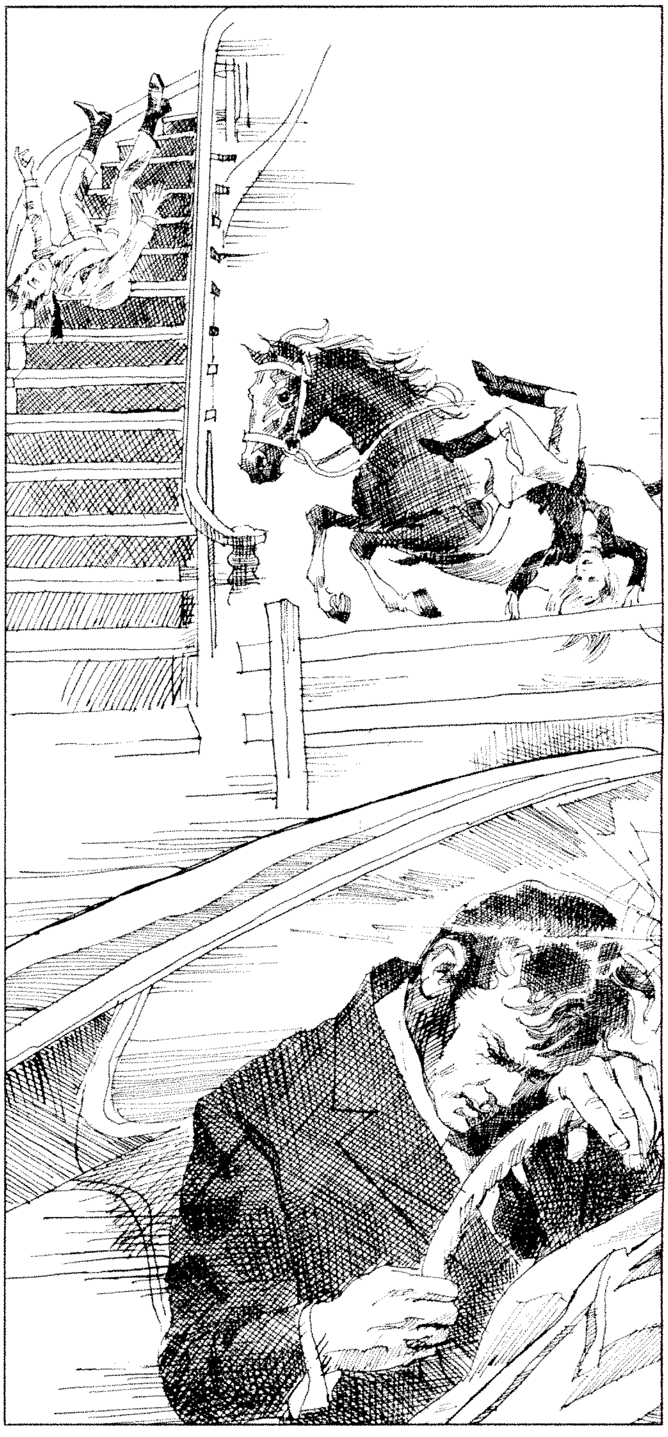
cerebral

expect it as a possible complication of primary or metastatic brain tumor.

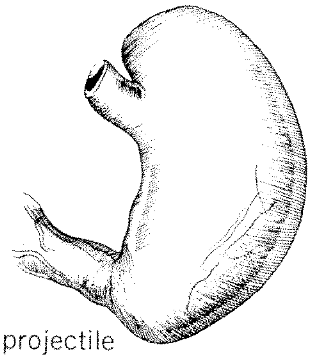


expect it in the presence of severe head injury.

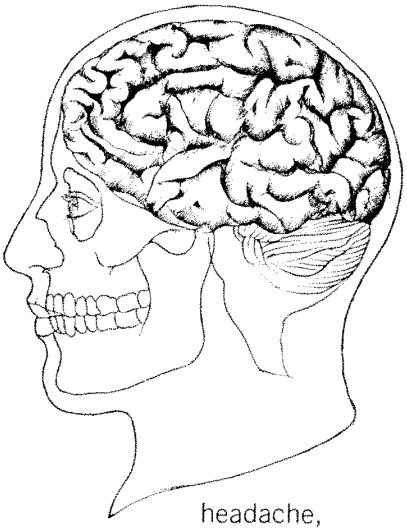


edema*

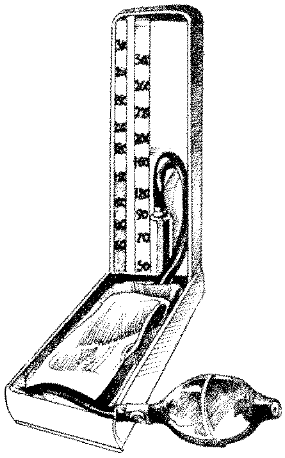
suspect it in the presence of signs and symptoms such as these:



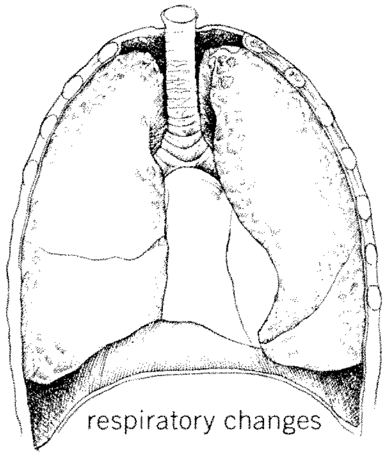
projectile
vomiting



headache,
altered consciousness

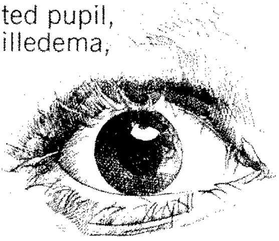


increased
blood
pressure

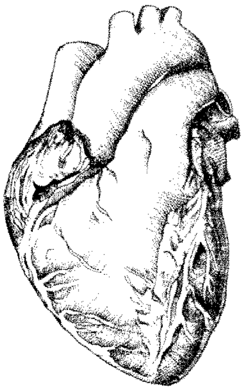


respiratory changes

dilated pupil,
papilledema,



unilateral or bilateral
abducens palsy



bradycardia

***Note: The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.**

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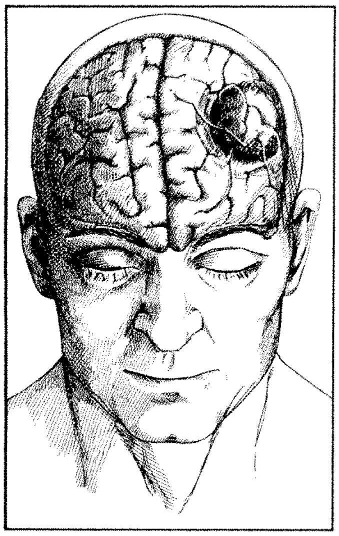

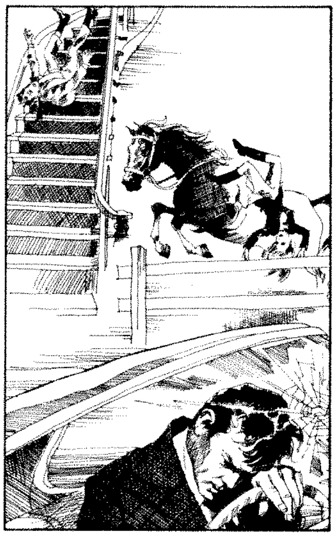

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**Ritchie WP: The emergency care of cerebral injuries,
J Lancet *86:*255, June 1966.**

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Dosage for cerebral edema

Injection DECADRON Phosphate is generally administered initially in a dosage of 10 mg dexamethasone phosphate (2.5 ml) IV followed by 4 mg dexamethasone phosphate (1 ml) IM every six hours until symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For the palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy should be individualized with either Injection DECADRON Phosphate or Tablets DECADRON (supplied as 1.5-, 0.75-, 0.5-, and 0.25-mg tablets). Two mg two or three times daily may be effective. The smallest dosage necessary to control cerebral edema should be utilized. The usual precautions in regard to corticosteroid therapy should be employed, and antacids, anticholinergic drugs, and diet measures to prevent gastrointestinal ulcer or hemorrhage should be considered. Please read the brief summary below, and consult full prescribing information before prescribing or administering.

Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

Oral Therapy—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

Parenteral Therapy—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: Oral and Parenteral Therapy—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

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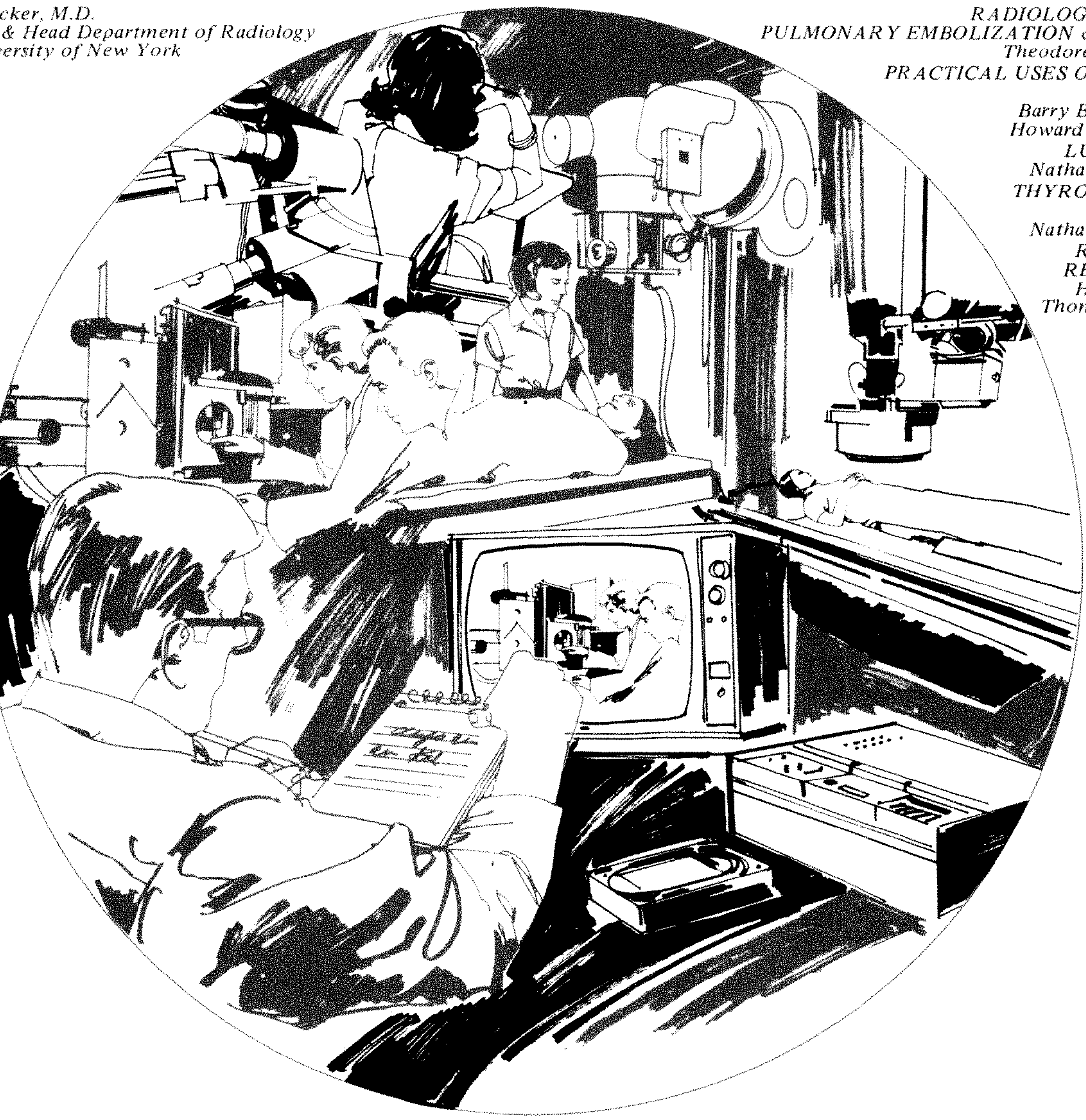

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Disseminated Intravascular Coagulation as a Complication of Abdominal Aortic Aneurysm Repair

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A retrospective review was done of all patients undergoing surgical repair of abdominal aortic aneurysm (AAA) on whom coagulation studies were obtained. Those patients with laboratory documented disseminated intravascular coagulation (DIC) were selected and their clinical records reviewed. This included 7 patients studied in the periods 1964–1965 and January 1971–July 1973. Of these 7 cases, 4 occurred in patients undergoing emergency operation for ruptured aneurysm and 3 were in elective cases. All 7 patients exhibited clinical evidence of abnormal bleeding, while 6 of the 7 progressed rapidly to renal shutdown. The seventh patient recovered spontaneously. Of the 6 patients with full blown clinical and laboratory evidence of DIC, 2 recovered. Both cases received heparin therapy and multiple hemodialyses. A third patient was started on heparin but died at 36 hours in heart failure. All 3 patients receiving heparin showed clinical cessation of abnormal bleeding and disappearance of soluble fibrin monomer complexes within 24 hours of starting therapy. The study suggests a higher incidence of DIC than has previously been appreciated in both the emergency and elective repair of AAA. The prompt recognition and treatment of this complication may reverse the abnormal intravascular clotting, minimize its more serious results and avoid futile and dangerous operative intervention.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC) is a clinical and laboratory syndrome characterized by two major phenomena: 1) The hemostatic mechanism is impaired owing to excessive utilization of platelets and coagulation factors, such as fibrinogen, factors V and VIII, secondary activation of the fibrinolytic system, and the presence of substances that inhibit the coagulation mechanism and platelet function. These changes may result in clinical evidence of diffuse hemorrhage. 2) Widespread deposition of fibrin thrombi in the microcirculation may occur, particularly in the kidney, and may contribute to some of the clinical findings in DIC, such as renal failure.

The number and variety of disease processes and etiologic agents recognized as causing intravascular coagulation have become legion. Arterial disease and arterial surgical procedures have been mentioned in review articles[6,26] and in case reports[1,5,8,9,20] as among the causes of the syndrome since 1967. However, recognition of DIC associated with abdominal aortic aneurysm (AAA) is rare. Indeed only three cases are documented in the literature at present.[13,14,24]

Several cases of DIC associated with surgical repair of abdominal aortic aneurysm have occurred in our institution in the recent past, suggesting that this complication is more common than formerly appreciated. This paper reviews our recent experience with abdominal aortic aneurysm repairs in which coagulation defects have been encountered, and explores the association of disseminated intravascular coagulation with that operation.

Materials and Methods

A retrospective review was done of the files of the coagulation laboratory at The Roosevelt Hospital from January 1971 through July 1973. During this period, coagulation studies on all pre-or postoperative surgical patients who were clinically or historically suspected of having coagulation deficiencies were performed only in this laboratory. Those patients with laboratory documented DIC who were treated from abdominal aortic aneurysm are reported in this study. Their records were

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reviewed with respect to historical data relevant to DIC, clinical presentation of the abdominal aortic aneurysm, preoperative therapy, intraoperative record, and postoperative course.

In the course of reviewing the coagulation laboratory material, two additional cases studied by the same laboratory personnel at The Presbyterian Hospital were uncovered. Although these two cases do not contribute to our knowledge of the frequency of disseminated intravascular coagulation associated with abdominal aortic aneurysm, they are included for completeness.

Coagulation studies included one-stage prothrombin[18] and partial thromboplastin time,[17] fibrinogen level,[10] platelet count,[3] factors V and VIII,[25] profibrinolysin and fibrinolytic inhibitors,[15] and euglobulin lysis time.[2] The presence of fibrin monomer in plasma was detected by the ability of protamine sulfate to dissociate the monomer from soluble complexes resulting in fibrin strand or gelation.[21]

Two methods were used to determine fibrin split products on serum obtained by clotting whole blood in the presence of thrombin 100 units/2 ml blood and a fibrinolytic inhibitor and allowed to stand at room temperature for 24 hours. One method (Fi test) contains an antibody to fibrinogen itself while the other (Thrombo-Wellcotest) has antibody to fragment D and E.[16] Both methods involve agglutination of antibody coated latex particles by diluted serum. There is some cross reaction between the two tests.

Results

January 1971–July 1973

Five patients who were operated upon for abdominal aortic aneurysm at The Roosevelt Hospital from January 1971 to July 1973 developed disseminated intravascular coagulation, documented by coagulation studies.

Table 1 summarizes the preoperative and intraoperative clinical data on these five patients. All were in their seventh or eighth decades. Four presented to the emergency room within hours of the onset of abdominal and back pain and had clinical and operative findings of

TABLE 1. *Presenting Clinical Picture and Intraoperative Data*

Case	Age	Sex	Previous HX	Pre-op Shock	Operative Category	Pathology	Procedure	Time (Hrs)	Intraoperative Fluid Replacement	Significant Hypotension
						January 1971–July 1973				
1.	73	M	Known AAA (5 yrs)	No	Emergency	Ruptured AAA	Aorto-bilateral common femoral graft	4	4500 cc whole blood	Yes
2.	68	M	Known AAA (2 yrs)	Yes	Emergency	Ruptured AAA	Aorto-bilateral common iliac graft	4–1/2	7000 cc whole blood	15 min. Syst—60
3.	79	M	No serious illnesses, Pronestyl for cardiac arrhythmia	No	Elective	Distal aortic & bilateral common iliac aneurysm	Aorto-bilateral external iliac graft. Ligation hypogastrics, bilateral.	3–3/4	2000 cc whole blood	No
4.	70	M	Partial gastrectomy, hypertension, angina, bilateral calf claudication, heavy smoker	Yes	Emergency	Ruptured AAA	Aorto-bilateral common femoral graft.	4	6500 cc whole blood 10 units platelets	Syst 70–100 Entire case
5.	69	M	Hypertensive	Yes	Emergency	Ruptured AAA	Aorto-bilateral common iliac graft.	4	2500 cc whole blood 400 cc fresh frozen plasma	No
						1964–1965				
6.	68	M	Asymptomatic AAA	No	Elective	Distal aortic aneurysm	Aorto-bilateral external iliac graft.	4–1/2	2000 cc whole blood	No
7.	66	F	Tender AAA. Partial gastrectomy & hepatectomy 20 yrs prior for carcinoma of stomach. Liver function studies normal.	No	Elective	Distal aortic aneurysm	Aorto-bilateral common iliac graft.	4	3000 cc whole blood 8 gms fibrinogen	Yes

TABLE 2. *Postoperative Course*

Case	Immediate Post-op Events	Heparin RX	Course	Outcome
			January 1971–July 1973	
1.	Abdominal distension, hypotension requiring multiple transfusions renal shutdown	No	Explored 24 hours post-op for retroperitoneal bleeding.	Died 48 hours of continual bleeding, no autopsy.
2.	Renal shutdown, bleeding from venipuncture sites, wound.	No	Continued thrombocytopenia, persistent oozing, hemodialysis × 3.	Sepsis, RLL pneumonia, icteric. Died 8 days, no autopsy.
3.	Renal shutdown, oozing from venipuncture sites, wound.	Yes	Explored, post-op Day #2 for bleeding gastric ulcer; bleeding stopped. Hemodialysis × 13.	Recovered renal function, discharged after 6 weeks.
4.	Intraoperative bleeding, renal shutdown post-op.	Yes	Persistent hypotension pre-,intra-, and postoperatively; bleeding stopped.	Died 36 hours, congestive failure. Autopsy—fibrin thrombi, glomeruli.
5.	Abdominal distension bleeding from venipuncture sites, wound. Renal shutdown.	Yes	Pulmonary insufficiency requiring tracheostomy; bleeding stopped. Hemodialysis × 11.	Recovered pulmonary & renal function, Died 8 weeks of CVA.
			1964–1965	
6.	Intraoperative Postoperative course satisfactory except for some drop in hematocrit.	No	Uneventful recovery	Discharged, well.
7.	Intraoperative bleeding followed by hypotension and renal shutdown.	No	Hypotension, acidosis, continued bleeding, cardiac arrest	Died 24 hours, Autopsy—fibrin thrombi in glomeruli.

ruptured abdominal aortic aneurysm. The fifth patient underwent elective operation for asymptomatic aneurysm involving aorta and both common iliac arteries.

Three of the four patients with ruptured aneurysms were clinically in shock at admission and two remained so during significant periods of their emergency operation. The fourth patient with ruptured aneurysm and the patient undergoing elective repair experienced no significant hypotension from admission through operation.

All five patients underwent endo-aneurysmorrhaphy and replacement with a bifurcation graft. All procedures were from 3¾ to 4½ hours in duration. Blood replacement varied but exceeded 2,000 ml in all the ruptured aneurysms.

The postoperative courses of these five patients are summarized in Table 2. For each case there was evidence of abnormal bleeding during or after the operation and progressive renal shutdown despite vigorous therapy with diuretics and fluid replacement. Coagulation studies were obtained within 12 hours after the operation in all cases (Table 3).

All five patients showed severe thrombocytopenia. Fibrin monomer was detected in the plasma of all patients. Fibrinogen was decreased, and prothrombin time and partial thromboplastin time prolonged in 4 of 5 patients. Factor V was markedly decreased in the three patients in whom it was determined. Fibrin split products (FSP) in patient 5 were detected by the Thrombo-Wellcotest but not by the Fi test. The failure of the Fi test to detect FSP in sera from 24 hour old cloted blood early in the course of DIC has been noted previously.[28]

It can be seen that the only abnormal coagulation data for Case 2 were a thrombocytopenia, slightly prolonged prothrombin time, and positive fibrin monomer. We feel that fibrin monomer in the plasma is evidence of abnormal intravascular coagulation. Since Case 2 also exhibited the same clinical complex of abnormal bleeding

TABLE 3. *Coagulation Studies**

Case	1	2	3	4	5	6	7	Normal
Prothrombin Time (sec)	21.3	15.8	20	18.2	19.8	18	20	12–14
Partial Thromboplastin Time (sec)	94.3	31.5	>60	82.5	53.2	82	187	35–45
Fibrinogen (mg%)	122	234	60	104	146	124	112	200–400
Platelets/cmm	23,000	23,000	28,000	48,000	69,000	127,000	80,000	200,000–400,000
Factor V (% normal)	18%			25%	25%		20%	70–130
Factor VIII (% normal)				34%				50–200
Factor IX (% normal)				41%				60–140
Fibrin Monomer	Pos	Pos	Pos	Pos	Pos			Neg
Fibrin Split Products Fi test (μg/ml)			0		0			0
Thrombo-Wellco Test (μg/ml)					10			<5
Profibrinolysin (units)	1.6		0.7	2.3	2.3	2.7	1.1	3.7–6.2
Fibrinolytic Inhibitors (units)	0.3		0.5	1.0	1.0	0.7	0.2	2.4–5.4
Euglobulin Lysis Time (min)	200				300		60	>180

* Studies were obtained within 12 hours postoperatively.

from the wound and venipuncture sites and renal failure shown in the other 4 patients, we feel it is likely this patient had DIC, despite the paucity of abnormal laboratory data. He continued to have clinical evidence of excessive oozing from wound and venipuncture sites until his death on the eighth postoperative day.

All patients were transfused with large amounts of blood and were given platelets, fibrinogen and fresh frozen plasma as well. In addition 3 patients received heparin in a dosage of 5 units/kg of body weight/hour.

The serial changes in coagulation studies of the two patients (Cases 3 and 5) who survived the postoperative period are shown in Figs. 1 and 2 respectively. In both patients, prothrombin time and fibrinogen levels returned to normal ranges within 24–48 hours of the initial studies. Platelet count and profibrinolysin levels remained depressed for longer periods of time.

The presence of fibrin monomer and the course of heparin therapy are depicted in the charts. In Case 3, heparin was briefly discontinued shortly after its institution because of a bleeding gastric ulcer which was oversewn on the third postoperative day. Heparin was then reinstituted. In both patients, the presence of fibrin monomers disappeared 24 hours after the institution of heparin therapy, and reappeared only during the brief cessation of heparin in Case 3 as mentioned above. Clinical evidence of abnormal wound and venipuncture oozing had ceased within 24 hours of starting heparin. Both of these patients survived to recover their renal function after multiple hemodialyses.

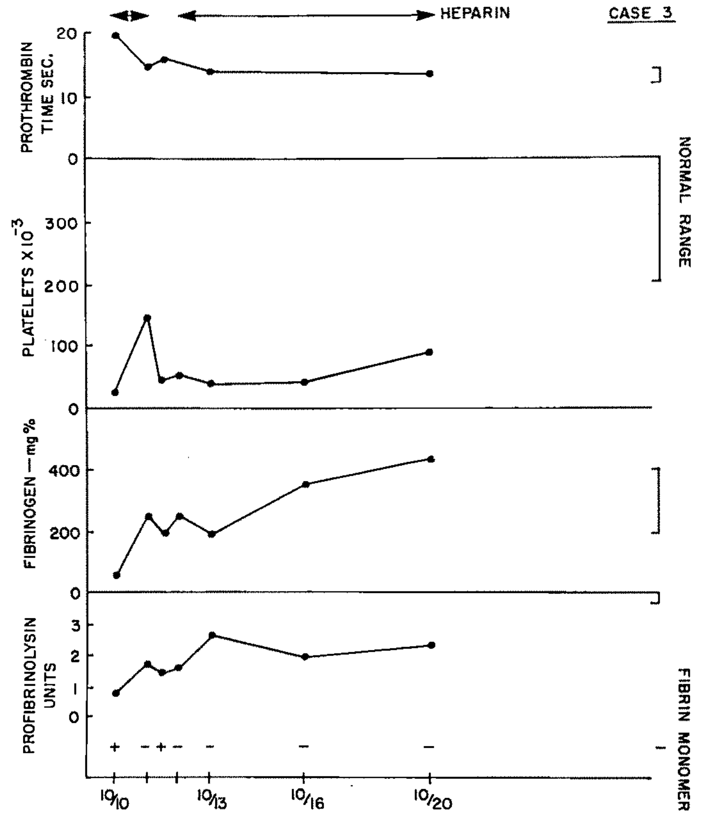

FIG. 1. Serial coagulation studies in Case 3.

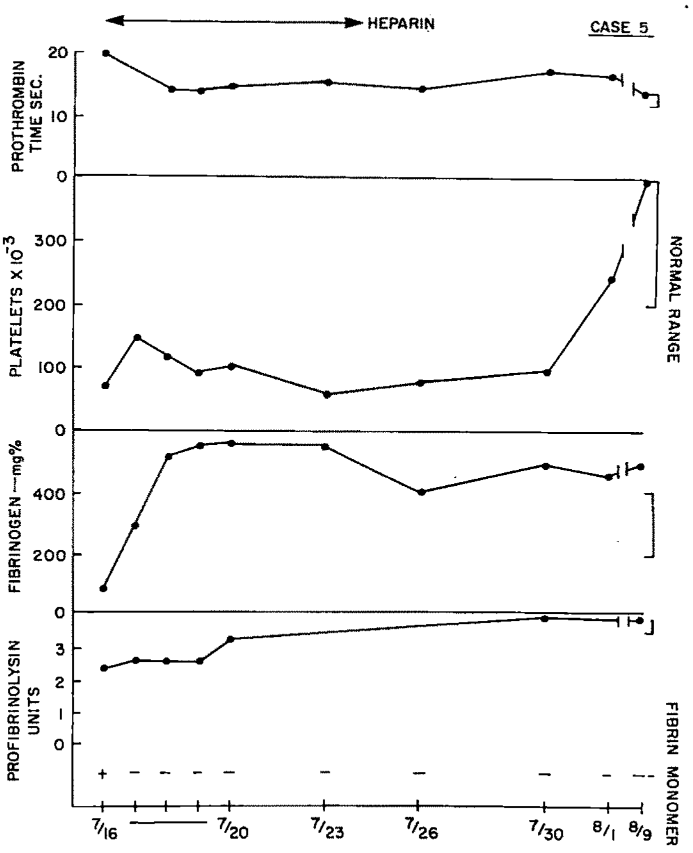

FIG. 2. Serial coagulation studies in case 5.

One patient, Case 4, died of cardiac and pulmonary failure 36 hours postoperatively. Heparin therapy had been instituted after DIC was detected, and abnormal clinical oozing had ceased. However, meaningful followup laboratory data could not be obtained before his early demise. Fibrin thrombi found in his kidneys at autopsy are shown in Fig. 3.

One patient, Case 1, died at 48 hours after a reexploration for continued clinical hemorrhage. This patient had received no heparin therapy and no followup laboratory data was obtained.

1964–1965

Two additional cases of DIC complicating abdominal aortic aneurysm repair were found. The pre operative, intraoperative and postoperative data are also summarized in Tables 1 and 2. Both cases were elective repairs with no obvious antecedent cause for a coagulation defect. Although Case 7 had a partial hepatectomy 20 years previously, her preoperative liver function tests were normal.

The presence of a coagulation defect was suspected in

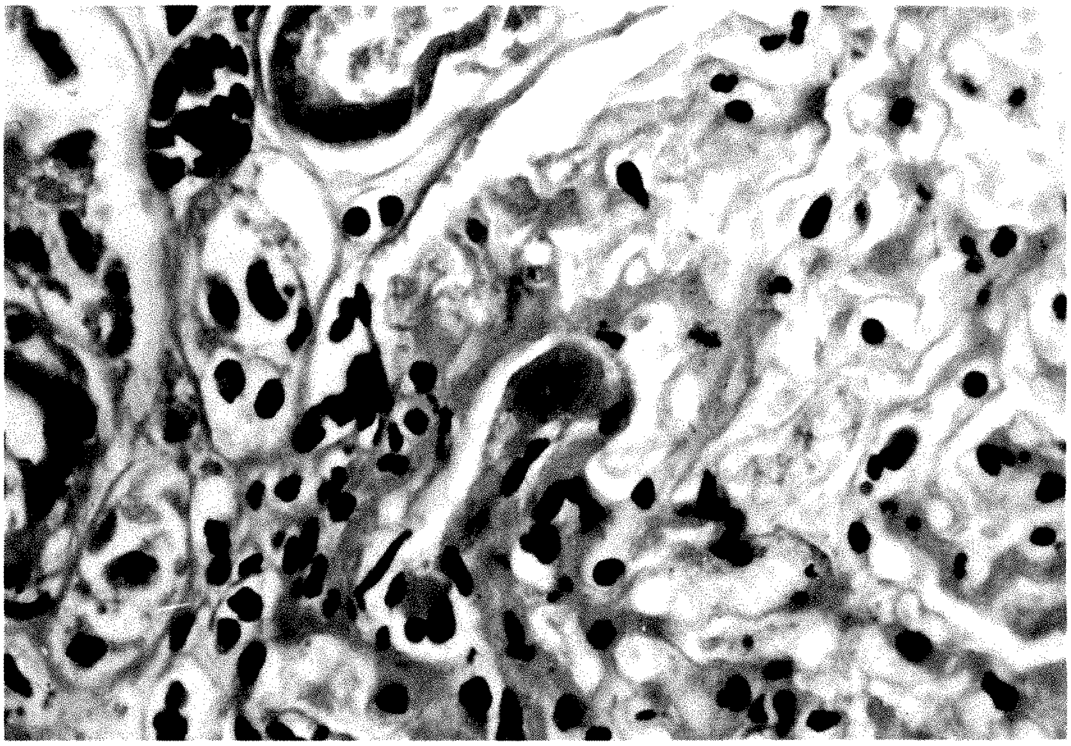

FIG. 3. High power view of glomerulus from autopsy material case 4. Glomerular basement membrane runs from top center to lower left. Convoluted tubules are at top left, glomerular capillaries to right with fibrin thrombus in center (H&E ×250).

each case by the occurrence of excessive bleeding during surgery. In one case, #6, bleeding did not become a major problem, and he recovered spontaneously. In the second case, #7, a significant amount of intra- and postoperative bleeding occurred. Although fibrin monomers were not studied, other coagulation findings were consistant with a diagnosis of DIC. In addition, fibrin thrombi were found in the glomeruli at autopsy.

Discussion

Since the late 1960's, arterial diseases and surgical procedures have been listed among the causes of intravascular coagulation in articles reviewing this particular coagulation defect.[6,14] A number of case reports have indicated disseminated intravascular coagulation as a complication of such diverse arterial problems as arteriovenous fistula,[20] thoracoabdominal aneurysms,[22] femoral aneurysms,[1,5] dissecting thoracic aneurysm,[1,5] and arteritis.[9] These cases frequently did not involve operative repair, and in several instances data on the exact relationship of the coagulation defect to the arterial problem are not well documented.

Only three cases of DIC associated with abdominal aortic aneurysm have been documented in the extensive literature dealing with these two conditions. In one case, presented in two separate papers,[9,13] DIC was documented preoperatively in an asymptomatic AAA that had been noted to be slowly enlarging. The coagulation abnormalities disappeared after operative repair. A second case was noted as a complication of surgical repair in one of 80 patients with ruptured AAA.[10] This latter case is the only recognition of DIC as a complication of operative repair in the numerous large series of abdominal aortic aneurysms reported in the last decade.[4,7,10,23,27,29] In a third study, an example of AAA was used by one of us (L.L.P.) in discussing intravascular coagulation.[14]

We reviewed the charts on 44 patients who had abdominal aortic aneurysms at our institution in the period January 1971–July 1973. Of these 44 repairs, nine were emergency procedures for ruptured AAA, while 35 were elective operations.

Of the 35 elective repairs there were two hospital deaths. One patient died at 2½ weeks of a CVA and the other at 10 days in cardiac failure. Since the three elective cases (3, 6 and 7) presented in this paper were the only patients done electively to have adequate coagulation studies, no conclusions can be drawn about the true incidence of DIC in elective aneurysm surgery. However, this documentation of DIC in three elective repairs suggests the possibility of a higher incidence of this complication in elective repair than was previously recognized.

Nine patients had emergency repairs of ruptured aneurysms from 1971–1973. Four are presented in this paper with documented DIC, two of whom survived the operation and complications. The other five cases were not studied for DIC and therefore the true incidence of this complication in repairs for ruptured aneurysms is not known. Three of the five died within hours of operation and two survived to be discharged. No conclusions regarding the importance of DIC in deaths following ruptured aneurysm repairs can be made. What does seem true, however, is that the incidence of DIC in repairs of ruptured aneurysms is at least 44% in this series, which again suggests a higher incidence than previously recognized.

That this association has not been reported in the large published series of abdominal aortic aneurysm repairs may be due to previous failure to recognize DIC. In one series, Darling[7] alludes to "generalized venous oozing" postoperatively in four of 60 repairs for ruptured AAA. In Darling's cases, as in 100 consecutive AAA repairs by Stokes and Butcher,[23] an unspecified number of patients suffered "acute tubular necrosis." Couch *et al.*[4] reported that excessive bleeding occurred in 18 of 101 repairs including two deaths with "clotting defects" since 1960. It is entirely possible that DIC accounted for some of these complications reported in the previous series. If this is the case, then prompt and detailed coagulation studies are indicated when these complications arise. If DIC is documented, we feel that the patients should receive heparin therapy and appropriate replacement of clotting factors. Re-exploration of these patients, as advocated by Darling and Stokes, is not indicated when evidence of DIC is present. Indeed such a procedure may be hazardous.

Most cases of DIC are attributable to the entrance of tissue procoagulants of various types in to the systemic circulation with subsequent activation of the clotting mechanism.[12] Other factors such as shock, stasis of blood flow, acidosis, endothelial cell damage and depressed reticuloendothelial function may play contributing roles. The mechanisms that account for the occurrence of DIC in the patients described in this paper are not clear at present although all of the above factors may be involved. As coagulation studies were not performed preoperatively, we cannot say whether the DIC in these patients is related to the AAA per se or to its operative repair. The demonstrations of DIC by Schnetzer in a stable thoraco-abdominal aneurysm,[22] preoperatively by Kazmier[9] in a slowly expanding AAA, and in an expanding femoral aneurysm by Berger[1] suggests the possibility that some activation of the clotting mechanism may occur preoperatively. This may be further enhanced by an operative procedure involving incision or excision of the wall of the aneurysm.

Straub and Kessler injected ^{131}I fibrinogen[24] and demonstrated the accumulation of radioactivity in an AAA by surface scan. They also demonstrated a large, radioactive fibrin mass within the electively resected aneurysm.

The diagnosis of DIC requires recognition of the hemorrhagic-thrombotic diathesis and its corroboration by appropriate coagulation studies. Laboratory evidence of DIC includes a decreased platelet count, prolonged prothrombin and partial thromboplastin times, and the presence of fibrin monomer. The fibrinogen level is usually decreased and other factors utilized in the coagulation process such as factor V, VIII and II (prothrombin) may also be decreased. Evidence of fibrin split products due to a secondary activation of the fibrinolytic system may also be found. Demonstration of fibrin thrombi as in Case 4 (Fig. 3) and 7 in our series, provides direct evidence of disseminated intravascular coagulation. The response to heparin therapy is further support for the diagnosis.

We feel that the treatment of choice for DIC is intravenous heparin. Heparin inhibits several stages of the coagulation mechanism, arrests the intravascular coagulation process and may help protect target organs from further deposition of fibrin thrombi.

Of the seven cases presented, one (Case 6) recovered spontaneously with no evidence of renal failure and no unusual therapy. The remaining six all developed renal failure as well as clinical abnormal bleeding. Heparin was administered to three of these patients with the cessation of clinical bleeding and disappearance of fibrin monomer from the plasma within 24 hours. Two survived after multiple hemodialyses. The third died in 36 hours of cardiac failure. Three patients received no heparin therapy. All three died and all three showed continued clinical evidence of abnormal bleeding until death.

Although this data is not conclusive on the point, it suggests that heparin may be of value in treating the abnormal intravascular coagulation and its clinical sequellae. This corresponds to the therapeutic approach we have adopted after experience in treating DIC associated with a wide variety of clinical diseases.

Once the diagnosis is made, we promptly treat with platelet concentrates and heparin, administered as a continuous infusion in a dose of 5 units kg/body weight/hr. Although this is a relatively small dose of heparin, we have found it to be effective in preventing further intravascular coagulation without the danger of severe hemorrhage that we have observed with the use of higher doses, particularly in the presence of thrombocytopenia.[28] We also replace fibrinogen and other depleted coagulation factors after heparin therapy is instituted.

Fibrinolytic activity is often demonstrable in association with DIC, but this is a secondary phenomenon in nearly every instance. The effect of the fibrinolysis associated with DIC is a salutory one, in that it acts to lyse fibrin thrombi in the target organs. Therefore, except in rare instances where extreme fibrinolytic activity can be demonstrated as the overwhelmingly preponderant defect in coagulation, the use of antifibrinolytic agents, such as epsilon aminocaproic acid (Amicar) is contraindicated in the treatment of post-operative bleeding after aneurysm repair. This caution is of particular importance when oliguria is present.

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Amino Acid Metabolism in Acute Renal Failure:

Influence of Intravenous Essential L-Amino Acid Hyperalimentation Therapy

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A solution of 8 essential 1-amino acids and hypertonic dextrose was administered to 5 patients in acute postoperative renal failure in a program of hyperalimentation designed to decrease the patient's catabolic state and to accrue certain metabolic benefits. A sixth patient receiving intravenous glucose alone served as a control. The pretreatment plasma concentrations of amino acids in all 6 patients did not differ significantly from normal; following intravenous essential amino acids at a dose of approximately 12.6 gm/24 hours, no significant elevations out of the normal range of these substances occurred. Since urinary excretion rates did not dramatically increase, urinary loss was excluded as a possible cause for the failure of increase of plasma concentrations. The results suggest that the administration of an intravenous solution of 1-amino acids and hypertonic dextrose is associated with rapid clearance from the blood of these substances and, with a failure of increased urinary excretion, indirect evidence of amino acid utilization for protein synthesis has been obtained. Histidine supplementation in patients with acute renal failure is probably unnecessary based on the lack of significant decreases in histidine concentrations in these patients.

METABOLIC COMPLICATIONS arising from the acutely uremic state result from both a loss of excretory capacity and increased catabolism. With accelerated gluconeogenesis which occurs in the starved patient with renal failure, breakdown of structural protein (lean body mass) causes an efflux of organic and inorganic metabolic products into the intravascular space. Morbidity and mortality often result from the excess concentrations of the latter, such as hyperkalemia, due mainly to cardiotoxicity. Little data are available, however, regarding the altered concentrations or metabolism of plasma amino acids during acute renal failure.

A heightened interest to the importance of nutrition in acute renal failure occurred when Dudrick and co-workers[10] reported the delivery of a hypertonic mixture of a nitrogen source and carbohydrate to provide total parenteral nutrition in a wide variety of patients in a program he called "hyperalimentation." Application of these techniques to the use of a Giordano-Giovannetti[11,18] diet for patients in renal failure was initiated by several independent investigators.[9,15,22] We have confirmed the BUN-stabilizing influence of such a dietary regimen, noted improved survival following acute renal failure in certain instances, and reported decreases in inorganic ionic substances following treatment with an intravenous solution of eight essential 1-amino acids and hypertonic glucose ("Renal Failure Fluid").[2-6] The metabolic fate of these intravenously-infused amino acids has not been studied to date in patients with acute renal failure, nor has the influence of specific dietary therapy been studied on the plasma concentration of amino acids.

The present study was undertaken to elucidate pos-

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TABLE 1. *Clinical Data in Six Patients with Postoperative Acute Renal Failure*

Pt.#	Age	Sex	Renal Diagnosis	Primary Illness	Operative Procedure	Outcome	Cause of Death	Treatment
1	62	M	A. T. N., acute pyelonephritis	Ruptured internal iliac artery aneurysm	Resection and grafting of aneurysm	L	—	RFF
2	31	M	A. T. N.	Septic cup arthroplasty	Revision of cup (shaft) arthroplasty	L	—	RFF
3	49	M	A. T. N., chronic pyelonephritis; nephrocalcinosis	Dissecting aneurysm of thoracic aorta	Resection and grafting (left heart bypass)	D	Renal (never recovered renal function)	RFF
4	61	M	A. T. N.	Arteriosclerotic coronary artery disease	Double aorto-coronary bypass grafting	L	—	RFF
5	72	M	Massive bilateral cortical necrosis, A. T. N.	Ruptured abdominal aortic aneurysm	Resection and grafting of aneurysm	D	Renal (never recovered function); massive gastrointestinal hemorrhage	RFF
6	61	F	A. T. N.	Congenital hip dislocation	Total hip replacement	L	—	glucose

A. T. N. = Acute Tubular Necrosis.
RFF = "Renal Failure Fluid" (8 essential 1-amino acids and glucose).

sible alterations in amino acid metabolism in surgical patients with acute renal failure before and during treatment with an intravenous Giordano-Giovannetti type of regimen.

Materials and Methods

The six adult patients selected for this study were derived from a larger group of patients suffering with a variety of disorders of nitrogen metabolism. These patients were selected from a patient population[1] treated over a two-year period with a solution of intravenous essential 1-amino acids and hypertonic dextrose ("Renal Failure Fluid"). The six patients (Table 1) had all sustained an acute renal injury consisting of acute renal tubular necrosis following an episode of hypotension and renal ischemia.

The "Renal Failure Fluid" (RFF)* solution (Table 2) was administered to five of the patients (Patients 1–5) within 96 hours of the onset of renal failure; the sixth patient (Patient 6) received a nitrogen-free solution of 50% dextrose with vitamins at infusion rates similar to the amino acid-treated group. All nutrient solutions were infused via a superior vena cava catheter inserted percutaneously into either the internal jugular or subclavian vein using gravity infusion at a constant rate for each 24-hour period as has been previously described.[3,5,6] The supportive management of these patients including the meticulous aseptic care of the hyperalimentation catheter has been previously described in detail.[19] Four of the six patients (Patients 2, 3, 4, 5) required peritoneal dialysis at some time during their treatment for acute renal failure but none of the patients received dialysis during the study period.

Following placement of the hyperalimentation catheter and confirmation of a central location by chest roentgenogram, infusion of the nutrient solution was initiated at 30 ml/hour throughout the 48-hour test period. Daily serum electrolytes and renal function studies were performed in addition to the plasma and urine amino acid determinations.

Within six hours prior to infusion with the nutrient solution, blood and urine samples for amino acid analysis were obtained during this pretreatment or "control" state. Once the intravenous infusion was initiated for at least 24 hours but not exceeding 48 hours, additional samples were obtained. Venous blood specimens were collected in tubes containing EDTA and the plasma

TABLE 2. *Composition of Essential L-Amino Acid and Hypertonic Dextrose Solution ("Renal Failure Fluid") Used for the Treatment of Acute Renal Failure at the Massachusetts General Hospital*

Components	Amount
Amino Acids	1.4
1-Isoleucine	1.4
1-Leucine	2.2
1-Lysine HCl	2.0
1-Methionine	2.2
1-Phenylalanine	2.2
1-Threonine	1.0
1-Tryptophan	0.5
1-Valine	1.6
Total	13.1 gm
Glucose	350 gm
Water	750 ml
Vitamins	
A	5000 USP units
B1 (Thiamine HCl)	25 mg
B2 (Riboflavin)	5 mg
B6 (Pyridoxine HCl)	7.5 mg
Niacinamide	50 mg
Panthenol	12.5 mg
3 (Ascorbic acid)	1.5 mg
D (Ergocalciferol)	500 USP units
E (dl-α tocopheryl acetate)	2.5 IU

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* Generously supplied as Freamine-E^{R} by the Medical Affairs Division, McGaw Laboratories, Glendale, California.

TABLE 3. *Renal Function Studies Obtained in Five Patients in Acute Renal Failure Treated with Renal Failure Fluid (RFF)*

Time	Blood Urea Nitrogen (mg/100 ml)	Serum Creatinine (mg/100 ml)	Urinary Volume (ml/24 hr)
Pretreatment	88.8 ± 12.1*	8.8 ± 1.4	470 ± 124
24 Hours After R.F.F.	101 ± 12.4†	10.0 ± 1.4†	269 ± 118†
48 Hours After R.F.F.	95.4 ± 9.7†	13.6 ± 1.5‡	528 ± 172†

* Mean ± S.E.

† Not significantly different from pretreatment values, i.e., $p > .05$.

‡ $p < .05$ (2-tailed).

separated by centrifugation. Deproteinization was accomplished by adding solid sulfosalicylic acid at approximately 40 mg/ml plasma. The supernatant was then stored frozen until analysis. Amino acids (tryptophan not determined) were measured on a semi-automated Technicon amino acid analyzer using a gradient buffer system.[21] Urine specimens were collected in 24-hour periods and stored frozen until analyzed by the same technique.

Results

Clinical and Renal Observations

Of the five patients treated with Renal Failure Fluid (RFF), three survived. The two patients who died (3 and 5, Table 1) survived for 86 and 26 days respectively, succumbing as a consequence of the failure to regain renal function. Post mortem examination in both of these instances revealed not only acute tubular necrosis, but evidence of severe, irreversible renal damage. The four total survivors (including the glucose-treated patient) had recovered normal renal function by the time of hospital discharge.

Each of the patients had developed oliguric acute renal failure at the time of treatment with the nutrient solutions. Although there were no statistically significant changes in either the blood urea nitrogen (BUN) or the urinary volume, evidence of continued severe renal failure was apparent by the progressive and significant daily increase in serum creatinine determinations suggesting the Giordano-Giovannetti effect of the solution on BUN concentrations (Table 3).[2–6]

Plasma Amino Acid Concentrations

Plasma amino acid concentrations in all six patients in acute renal failure during the control state did not differ significantly from the normal values of our laboratory (Table 4). Although there were decreases in the mean values of threonine, serine, glutamine, glycine, methionine, isoleucine, histidine, and arginine, these changes were very slight and were not substantially out of normal range. Slight increases in glutamic acid, valine, α-aminoadipic acid, cystine, leucine, and phenylalanine were also observed but, similarly, these increases were not significantly different from the normal values. There were significantly large quantities of 3-methylhistidine in the plasma in four of the patients.

Of the seven essential amino acids assayed in this

TABLE 4. *Plasma Amino Acid Concentrations in Five Patients with Acute Renal Failure*

Amino Acids	Normal Range (N = 10)	Pretreatment*	24–48 Hours After Treatment	Mean Change	P less than†
Taurine	.59–3.24	1.965 ± .055	1.205 ± .307	−.759 ± .330	.1
Threonine	1.32–2.97	1.195 ± .216	1.070 ± .203	−.125 ± .134	.4
Serine	1.19–2.63	.970 ± .010	.751 ± .028	−.220 ± .111	.1
Glutamine	3.26–8.97	1.807 ± .574	2.039 ± .718	.232 ± .349	.5
Proline	1.34–5.01	1.267 ± .202	1.536 ± .165	.269 ± .053	.1
Glutamic Acid	.47–1.35	1.629 ± .515	2.025 ± .192	.396 ± .379	.3
Citrulline	.37–1.05	1.254 ± .714	.196 ± .010	−1.058 ± 1.023	.4
Glycine	1.03–2.66	.905 ± .125	1.140 ± .232	.25 ± .280	.4
Alanine	2.54–5.98	2.195 ± .287	1.881 ± .376	−.314 ± .407	.4
α-Amino-Adipic Acid	.10–.39	.324 ± .040	.184 ± .022	−.140 ± .025	.1
Valine	2.28–3.36	3.498 ± .293	2.359 ± 246	−1.138 ± .192	.001
Half Cystine	.95–2.25	2.740 ± .830	2.464 ± .672	−.277 ± .406	.5
Methionine	.34–.52	.282 ± .020	.461 ± .062	.179 ± .059	.025
Isoleucine	.67–1.09	.614 ± .073	.383 ± .060	−.231 ± .102	.05
Leucine	1.43–2.13	2.749 ± .362	2.008 ± .347	−.741 ± .696	.3
Tyrosine	.82–1.79	1.205 ± .137	1.329 ± .138	.125 ± .153	.4
Phenylalanine	.86–1.27	1.675 ± .122	2.169 ± .132	.494 ± .080	.005
Ornithine	.66–1.35	1.198 ± .194	.802 ± .113	−.395 ± .104	.025
Lysine	2.18–3.95	2.469 ± .310	2.461 ± .312	−.009 ± .272	.7
Histidine	1.33–1.82	1.151 ± .118	1.095 ± .124	−.056 ± .144	.7
3-Methyl Histidine	0	.873 ± .094	.901 ± .046	.028 ± .100	.8
Arginine	.99–2.74	.687 ± .106	.470 ± .062	−.217 ± .237	.5

* Mean ± the standard deviation.

† Student's t-test for paired data, two-tailed.

study, there were no substantial increases in the plasma concentrations outside of the normal range following treatment with RFF. That is, although the minor increases in methionine and phenylalanine were statistically significant, the exogenous administration of these amino acids in the from of RFF did not elevate plasma levels outside of the normal range. There were paradoxical *decreases* in the plasma concentration of valine and isoleucine following RFF infusion compared to control concentrations (Table 4).

Urinary Excretion

Because of the continued low urinary output in the six patients during the study period, the total 24-hour urinary excretion of all amino acids was extremely small. In each of the five patients treated with RFF, treatment was associated with a *decrease* in urinary excretion of the seven measured amino acids following treatment (Fig. 1). In these patients, the mean 24-hour urinary excretion of these seven amino acids were: threonine, undetectable; valine, 3.58; methionine, 5.78; isoleucine, 2.78; leucine, 4.01; phenylalanine, 3.84; and lycine, 7.09 mg/24 hr. Although the total urinary excretion of these seven amino acids was greater in the five patients treated with RFF (mean 24-hour urinary excretion equals 27.01 mg; range 2.16 to 33.09) compared to patient #6 treated with dextrose alone (24-hour urinary excretion of the seven amino acids equals 9.99 mg), the rather minimal excretion rates compared to the total administered dose of the amino acids of 12.6 grams[*] in 24 hours yielded net urinary loss of less than 0.2%.

Discussion

The clinical efficacy of an intravenous Giordano-Giovannetti diet in patients with acute renal failure has been documented with regard to the effect of controlling life-threatening ionic imbalances,[3] maintenance of adequate nutrition by administration of this diet of high biological value,[1,6] and improved survival in certain instances of acute renal failure studied under a double-blind, controlled prospective protocol.[4,5] To date, only indirect evidence of the administered amino acid utilization and incorporation into lean body mass was suggested by the diminution in serum potassium, phosphate, and magnesium concentrations combined with a decrease in BUN to creatinine ratio,[3] and the slower rate of rise of BUN itself also suggesting the possibility of re-utilization of urea as a non-protein source of intracellular protein synthesis.[11,13]

The results of the present study lend further indirect evidence to the hypothesis of utilization of this intravenous synthetic amino acid diet for protein synthesis. Our observations that the resting plasma concentrations of free amino acids were indistinguishable from values predicted from our laboratory for normal adults are in accord with previous observations in chronicly uremic patients.[8,18]

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[*] Based upon infusion rates of 30 ml/hr × 24 hr.

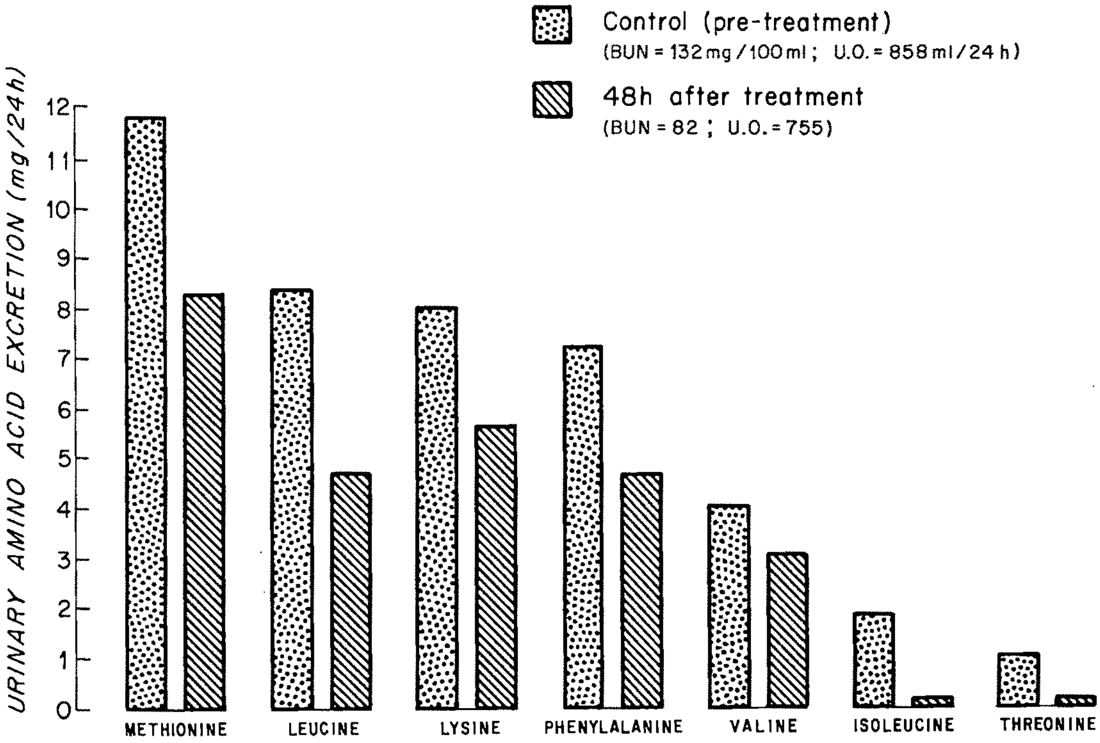

FIG. 1. Urinary excretion of essential amino acids in a 49-year-old man who developed acute tubular necrosis following resection of a dissecting thoracic aortic aneurysm. Despite essentially no change in renal function during the 48-hour interval of therapy, the total urinary excretion of the seven measured amino acids actually decreased despite administration of approximately 25 grams of amino acids during this period.

The results of earlier studies of plasma amino acid concentrations in patients with chronic uremia indicated a lack of consensus regarding the degree of abnormality, if any, which may exist.[8,18,20] In the acutely uremic patients in the present study, we failed to confirm consistent differences from normal patients with the exception of finding substantial quantities of 3-methylhistidine in four of six patients.

Administration of RFF in amounts approximately equal to the "safe" levels recommended by Rose *et al.*[17] had no consistent effect on the concentration of any measured amino acids. This apparently rapid clearance of administered amino acids by patients with acute renal failure confirms earlier results of a study in which a protein hydrolysate was infused in patients with chronic uremia[8] and a rapid decrease from 25 to 60% in plasma concentrations of all amino acids except tyrosine was observed within 150 minutes.

An alternative explanation for the apparently rapid clearance from the blood of the administered amino acids would be accelerated urinary excretion. This was predicted to be unlikely because of the acute renal tubular damage in these cases. The total quantity of amino acid excretion was extremely low, confirming over 99% apparent utilization of the administered substances. Less likely alternative explanations might include accumulation in the extravascular space or excretion via the gut or in sweat, but there are no data to support these contentions. Additionally, progressive decreases in glomerular filtration rate might have accounted for the low urinary excretion of amino acids, but this should have been reflected by increasing plasma concentrations.

Since Giordano and co-workers[12] observed that the addition of small amounts of histidine to a low-nitrogen diet was associated with an increased rate of amino acid conversion into hemoglobin, histidine has been considered by several investigators to behave as an essential amino acid in uremia. In addition to the evidence that histidine appears to be essential in newborn infants,[14] other investigators have supported the concept that histidine may be "essential" in patients with chronic renal failure.[7,15]

It is significant that none of the reports which advocate using exogenous histidine in uremic patients studied postoperative acute renal failure. The present report indicates that although plasma histidine concentrations were slightly depressed within the early phase of acute renal failure, these changes did not change substantially following treatment with the eight "essential" amino acids. These data suggest that at least during the early phase of acute renal failure, there appears to be no significant dimunition in plasma concentrations of histidine and, therefore, that histidine reserves or capacity for synthesis is not significantly impaired. Furthermore, since there is abundant evidence that the use of a solution of eight amino acids (excluding histidine) has resulted in apparent urea re-utilization and protein synthesis, the addition of histidine to patients with acute renal failure does not appear to be necessary. Since the addition of even minute amounts of non-essential nitrogen such as might exist in histidine supplements would predictably decrease the rate of urea re-utilization,[16] it is concluded that histidine should probably not be added to the short term hyperalimentation regimen to patients with reversible, acute renal failure.

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Bile Production in Fasted and Fed Primates

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Previous experiments have suggested differences in the bile salt independent flow rate between monkeys and dogs, and in the ability of bile salt secretion to influence bile flow. The present study was performed to determine whether the availability of food could have influenced these results. Bile flow and bile salt secretion rates were studied in fasted and fed primates. In the fasting experiments, sodium cholate, sodium taurocholate, and monkey bile were infused into the duodenum; only sodium cholate was infused in the feeding experiments. The results showed that bile flow was linearly related to the bile salt secretion rate in both fasting and feeding animals. Bile salt independent flow is extremely variable during fasting and is increased and stabilized by feeding. These studies indicate that the differences found in previous experiments are probably attributable to variations in experimental design.

Recent advances in the understanding of bile production may soon permit measurement of the different components of bile flow, in various types of biliary tract obstruction, and in other diseases of the liver or bile ducts. However, certain important differences in experimental findings have occurred, which may make such analyses difficult. These differences, which are attributable to variations in species or methods of study, are outlined below, and have been mentioned in a recent review of the subject.[15]

Intravenous infusion of bile salts, producing a steady rate of bile salt secretion by the liver, is associated with fluctuating bile flow in the fasted dog.[12] The fluctuation in bile flow is eliminated, if anticholinergic agents are infused concurrently with the bile salts.[6] Linear correlation between bile flow and bile salt secretion has been demonstrated under these conditions, by varying the rate of bile salt infusion.[6] Extrapolation of the relationship between bile salt secretion and flow suggested that bile flow was negligible at very low bile salt secretion rates.[6] Dowling[2] studied the effect of bile salt secretion on bile flow in the fed rhesus monkey. Linear correlation between bile salt secretion rate and bile flow was observed, although anticholinergic agents were not administered. At very low bile salt secretion rates, there was still considerable bile flow. It is not clear why anticholinergic agents are necessary to demonstrate the linear relationship between bile flow and the bile salt secretion rate in the dog, but not in the monkey, or why large bile flows occur at low bile salt secretion rates, in the monkey, but not in the dog. Although these differences could have been due to species variation, it seemed possible that they were related to the selection of fasted or fed models.

Nahrwold studied the effect of increasing bile salt secretion rate on bile flow, by infusing bile salts into the duodenum, in both fasting and fed dogs.[5] Bile flow was not affected in the former, but a significant increase occurred in the latter. It is difficult to explain why the fasted dogs in this experiment had no increase in bile flow, when the bile salt secretion rate was increased, since both Wheeler[6] and Dowling[2] demonstrated a good correlation between bile flow and the bile salt secretion rate. Furthermore, there was an appreciable bile flow at low bile salt secretion rates in both fasted and fed dogs in Nahrwold's experiments,[5] a finding similar to that in fed monkeys,[2] but different from that in other fasted dogs.[6]

The purpose of the present experiment was to deter-

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mine whether the described differences were related to species variation, or to other factors, such as the availability of food. The experiments of Wheeler[6] and those of Nahrwold,[5] both conducted in the dog, suggested that factors, other than species variation, accounted for the differences. It was hoped that clarification of these differences would help in the planning of studies of abnormal states affecting the liver and bile ducts.

Methods

Animal Model

Female rhesus monkeys (4–6 kg) were adapted to restraining chairs. They were fed monkey biscuits (Teklad Inc.) 30 gm/kg/day and housed in a room with diurnal variation in lighting. Room lights were on from 7 A.M. to 7 P.M. daily.

At operation, the supraduodenal bile duct was divided and the lower end was closed. The upper end of the bile duct was intubated in order to allow collection of all bile produced by the animal. A tube duodenostomy was also performed. The cystic duct was divided and tied, and the gallbladder aspirated. The procedure was similar to that described in detail by Dowling.[2]

Two weeks were allowed for recovery from the surgical procedure. During this period, the combined bile duct and collecting tube dead space was measured by the BSP method of Barber-Riley.[1] In the second week of the recovery period, the enterohepatic circulation of bile salts was maintained by constant intraduodenal bile salt infusion (Sodium cholate, 6–8 mmoles/24 hrs).

Infusion Solutions

The sodium cholate infusions were made from a commercial preparation (Sigma). This material was more than 95% pure by GLC. Solutions were prepared in distilled water to contain 1.0 mmole, 2.0 mmoles, 4.0 mmoles, 6.0 mmoles, or 8.0 mmoles/45 ml. Sodium chloride was added to the bile salt to produce solutions which were approximately isotonic (range 275–295 mOs/l Advanced Instruments Osmometer).

"Sodium taurocholate" (Sigma) was shown to be a crude preparation, containing approximately 60% sodium taurocholate and a variety of other conjugated bile acids, by GLC and TLC. The crude bile salt was used to make solutions containing 2.0 mmoles, 4.0 mmoles or 8.0 mmoles/45 ml.

The monkey bile used had been obtained during intraduodenal sodium cholate (Sigma) infusions in several monkeys. The bile contained 90% cholic acid and 10% chenodeoxycholic acid, by GLC. The bile acids were more than 90% conjugated, mostly with glycine (TLC). The bile was frozen at −20 C until the day of the experiment.

Experimental Procedure

Fasting Experiments. Each animal was given monkey biscuits (30 gm/kg) and water in the late afternoon (4–5 P.M.), on the day before a study. Two hours later, any remaining biscuits and water were removed. The intraduodenal bile salt, or monkey bile infusion was started at 5 P.M. and continued throughout the night and the next day, at one rate. A syringe pump (Harvard Apparatus Co.) and a roller pump (Holter Co.) were used to administer the bile salt solutions and monkey bile respectively. Bile sampling was started at 8 A.M. and continued to 4–5 P.M. The animals were then fed again and a new infusion rate established.

The sodium cholate was infused at a rate of 6.0 mmoles, 4.0 mmoles and 2.0 mmoles/24 hr, on three successive days in five animals; the volume infused on each day was 45 ml. Isotonic saline (45 ml/24 hr) was infused on the fourth day. In one animal, (C), sodium cholate was infused at 8 mmoles/24 hr, instead of 6.0 mmoles/24 hr. In two animals receiving sodium chloride infusions, an extremely slow bile flow was recorded. Since spontaneous biliary tract obstruction had occurred during very slow bile flows in previous experiments, the saline infusions were discontinued at very slow bile flows and sodium cholate infused at 1.0 mmole/24 hr. on a subsequent day. The entire experiment (four days of sampling) was repeated in all five animals, from several days to several weeks later. In some animals a third experiment was performed. The number of experiments done in each animal is shown in Table 1. Bile flow and bile salt concentrations were measured in each sample. Sodium taurocholate was infused at the rate of 2.0 mmoles, 4.0 mmoles and 8.0 mmoles/24 hrs. on three successive days in three animals. These experiments were repeated several weeks later in two of the animals. Monkey bile was infused on three successive days at 50 ml, 100 ml, and 200 ml/24 hr (approximately 2.0 mmoles, 4.0 mmoles, and 8.0 mmoles/24 hr) in each of four animals. The experiment was repeated several weeks later and in one animal it was repeated on a third occasion.

Feeding Experiments. The animals were fed 10 gm monkey biscuits and 30 ml water every two hours

TABLE 1. *Number of Experiments in Each Animal (Each Experiment Done over Three or Four Infusion Days)*

			Animal		
Fasting Experiments	A	B	C	D	E
1. Sodium Cholate	3	3	3	3	2
2. Sodium Taurocholate			1	2	2
3. Monkey Bile	3	2	2	2	
Feeding Experiments					
1. Sodium Cholate	1		2	1	1

throughout the day, beginning at 7:30 A.M. At 5 P.M. they were given only 20 gm/kg monkey biscuits, so that the total daily intake was approximately equal to that of the fasting group. The study was otherwise conducted as for the fasting experiment, except that only saline or sodium cholate infusions were used. In three animals, three infusion rates were used over three successive days. In a fourth animal (C), the study was continued over six days (three rates, two days at each rate). The feeding experiment was performed before the fasting experiments in one animal, between the fasting experiments in one animal and following the fasting experiments in two animals.

Bile Sampling Technique

In order to minimize errors due to bile duct and tubing dead space, the technique described below was adopted. Bile flow was calculated from the volume of bile produced during a sampling period. Chemical composition was determined in bile samples collected in the following manner. The volume of bile equal to the dead space volume, produced at the beginning of the first daily sample, was discarded. An identical volume, obtained from the initial outflow in the second sampling period, was added to the first sample. During the third and subsequent sampling periods, the initial outflow equal to the dead space volume was also added to the previous sample. Collection was continued at the end of the day to collect the dead space volume for the final sample.

TABLE 2. *Fasting Experiments: Bile Flow and Bile Salt Secretion Rates on Four Successive Days During Sodium Cholate Infusions (Animal A)*

Day	Infusion	Bile Flow ml/24 hr	Bile Salt Secretion mmoles/24 hr
1.	6 mmoles/24 hr sodium cholate	117.6	5.9
		117.6	5.7
		106.0	5.8
		110.4	5.5
		121.6	5.8
		142.4	6.8
2.	4 mmoles/24 hr sodium cholate	156.0	5.4
		153.6	6.0
		144.0	6.0
		115.2	4.8
		103.2	4.7
		70.4	4.0
		96.0	5.3
3.	2 mmoles/24 hr sodium cholate	108.0	4.5
		129.6	4.4
		101.6	3.1
		117.6	3.2
		99.8	2.6
4.	Saline	100.8	1.3
		67.2	1.1
		91.2	1.4
		72.0	1.1

Chemical Analyses

Bile salt concentration was measured by the enzymatic method.[2] Bile BSP concentration was determined as described by Wheeler.[13] To measure conjugated and unconjugated bile salts, undiluted bile (10 μl) was applied to silica Gel G thin layer chromatograms and developed with toluene: glacial acetic acid: water. 50:50:10 (v.v.v.).[11] Each sample was run on two lanes. One lane was stained with phosphomolybdic acid spray. The unstained lane was divided into conjugated and unconjugated areas, each area scraped, and the silica gel washed with methanol (10 ml). An aliquot of the methanolic solution was evaporated to dryness at 70 C. Methanol (0.1 ml) was added and bile salt concentration determined. The internal standards for conjugated and unconjugated bile salts (Supelco) were pure by GLC.

Gas liquid chromatography* of standards and infusion solutions was performed by methods recently described.[16]

Statistical Methods

Results were analyzed for difference by the Wilcoxon rank test. Bile flow was plotted against the bile salt secretion rate, and linear regression lines and correlation coefficients calculated. The standard error of the estimate (S.E.E.), a measure of vertical dispersion or scatter about the linear regression line, was also determined.

Results

Fasting Experiments

Bile Flow. Considerable variation in bile flow was observed during each experimental day, in all three types of infusion. Peak flow rates occurred at random times during the eight hour sampling period. The variation is shown in one representative four-day experiment (Table 2).

Bile Salt Secretion Rate. Variation in the bile salt secretion rate also occurred, but usually was less than that seen in the bile flow (Table 2). The bile salt secretion rate at the highest rates of infusion (6–8 mmoles/24 hrs) was usually the same as the infusion rate (±1.5 mmole/24 hr). At the lower infusion rates, the bile salt secretion rate was 0–2 mmoles/24 hr above the infusion rate, probably due to the contribution from hepatic synthesis which would be high at the low infusion rates. In some samples, the bile salt secretion rate differed from the infusion rate by 3–4 mmoles/24 hr. The bile salt secretion rate is equal to the hepatic bile salt synthesis rate during saline infusions when no bile salts are being absorbed from the intestine. The bile salt secretion rate showed little variation during saline infusions (Table 2), indicating that the bile salt synthesis rate was fairly steady. No differences in the results for bile flow or bile salt secretion rate were found between initial experiments and subsequent experiments done weeks later. This demonstrates that the results of studies commenced in the third week after surgery were not related to a failure to recover from the operative procedure.

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* Courtesy of Drs. M. M. Fisher and I. M. Yousef.

Bile Flow to Bile Salt Secretion Rate Relationship. Bile flow was plotted against the bile salt secretion rate, as previously described[12] (Figs. 1–3). In each case, there was an increase in bile flow as bile salt secretion rate increased. At any particular bile salt secretion rate, there was a large fluctuation in bile flow. The extent of this fluctuation was similar across the whole range of recorded bile salt secretion rates, in those studies in which the most data was gathered (three or more experiments at one infusion rate, figs. 1A-D and 3A). The data fell roughly between parallel lines (not shown) with no tendency for convergence of the lines at low bile flows. When only one or two experiments were performed at one infusion rate, the fluctuation of bile flow was not always similar at all bile salt secretion rates; neither was it consistently greater at high, medium or low bile salt secretion rates.

Linear regression analysis (Table 3) showed a highly significant correlation (usually $p < 0.001$) between the bile flow and the bile salt secretion rate. The large dispersion of the data from the linear regression line is demonstrated by the high values for the S.E.E. (Table 3). The mean bile salt independent flow[*] is defined by the Y-axis intercept of each linear regression line. The large fluctuation in bile flow at any bile salt secretion rate (vertical dispersion), suggested that in individual samples there was considerable variation from this mean bile salt independent flow.

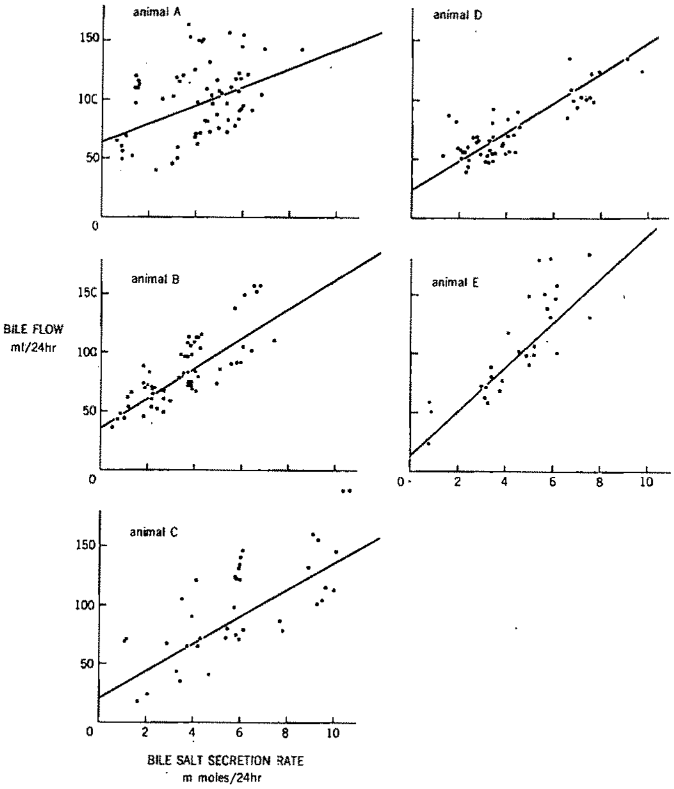

FIG. 1. Fasting experiment. Bile flow vs. bile salt secretion rate in samples obtained from animals receiving intraduodenal sodium cholate infusions. Line shown is linear regression line.

Conjugation of Bile Salts. During the sodium cholate infusions, the bile salts in the bile collected from the five animals were 87%–95% conjugated, except in one animal (A), in which the bile salts were 72–77% conjugated. During the bile and sodium taurocholate infusions, the bile salts were almost 100% conjugated, again with the exception of animal A (70–90%). Since the bile salts in the latter two infusions were more than 90% conjugated, it is suggested that this animal was deconjugating the infused bile salts, either in the intestine or in the bile, due to bacterial contamination. There was no correlation between the degree of conjugation and the fluctuations in bile flow at any bile salt secretion rate observed in the fasting experiments.

Feeding Experiments

Bile Flow. Bile flow was less variable during each experimental day in the feeding experiment than in the fasting experiment (Table 4). When variations in flow occurred, they were usually well related to changes in the bile salt secretion rate. Bile flow was increased during the feeding experiments.

Bile Salt Secretion Rate. The relationship between the bile salt infusion rate and the bile salt secretion rate was similar to that seen in the fasting experiments, except that large differences between the two rates, occasionally observed in the fasting experiments were rare in the feeding experiments.

Bile Flow to Bile Salt Secretion Rate Relationship.

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[*] The term bile salt independent flow used in this study indicates that part of the total collected bile flow, not dependent upon bile salt secretion. It does not indicate that the flow originates exclusively from the bile ductule or the canaliculus. Nor does it account for any portion of flow, which is independent of bile salt secretion, and which is absorbed in the ductule, since that would not be found in the total collected flow. The use of the term bile salt independent flow and the method of detection of this flow, in the studies cited in the introduction, are identical to the term and method in the present study. The portion of bile salt independent flow reabsorbed in the bile ductule may be estimated using canalicular clearance techniques,[4,14] but since the purpose of the present experiment was to explain the differences in the studies described, canalicular clearance techniques were not used here. The values for the slopes and Y-axis intercepts are presented for completeness. The significance of these values is limited by the scatter of the data and the presence of unconjugated cholic acid in the bile during cholic acid infusions.

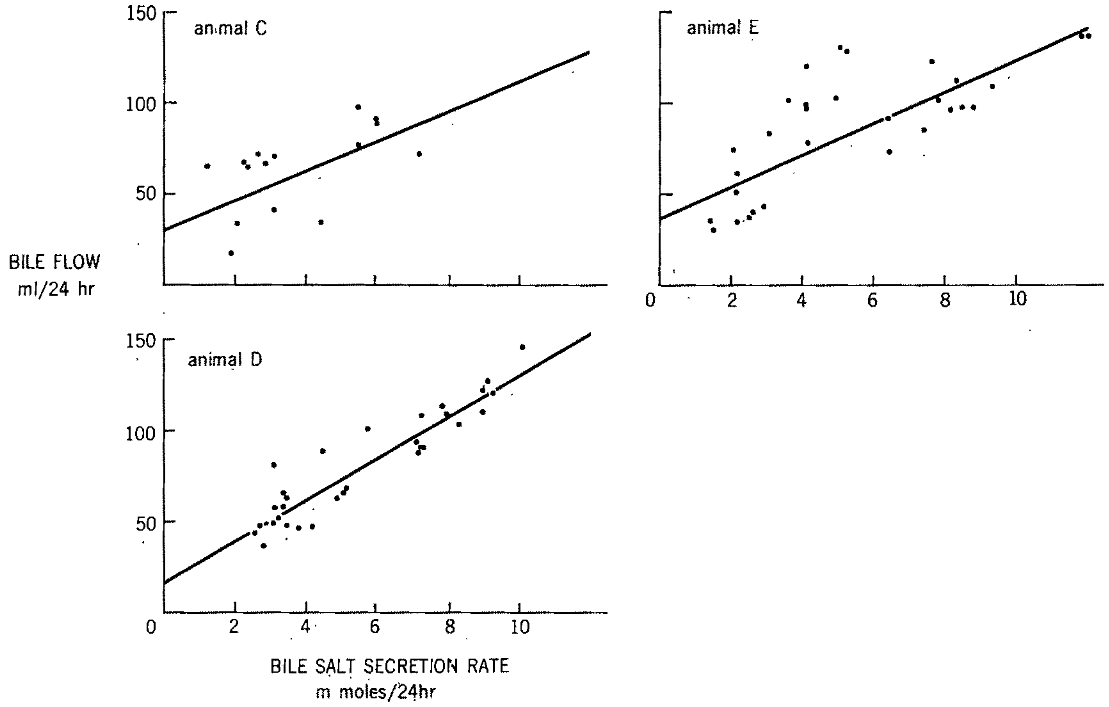

FIG. 2. Fasting experiment. Bile flow vs. bile salt secretion rate in samples obtained from animals receiving intraduodenal sodium taurocholate infusions. Line shown is linear regression line.

Bile flow was plotted against the bile salt secretion rate (Fig. 4). There was an obvious increase in bile flow as the bile salt secretion rate increased. In comparison with the fasting studies, little fluctuation was observed in the bile flow at any particular bile salt secretion rate. The linear regression data is shown in Table 5. The linear correlation coefficients were highly significant ($p < 0.001$) and significantly higher than the linear correlation

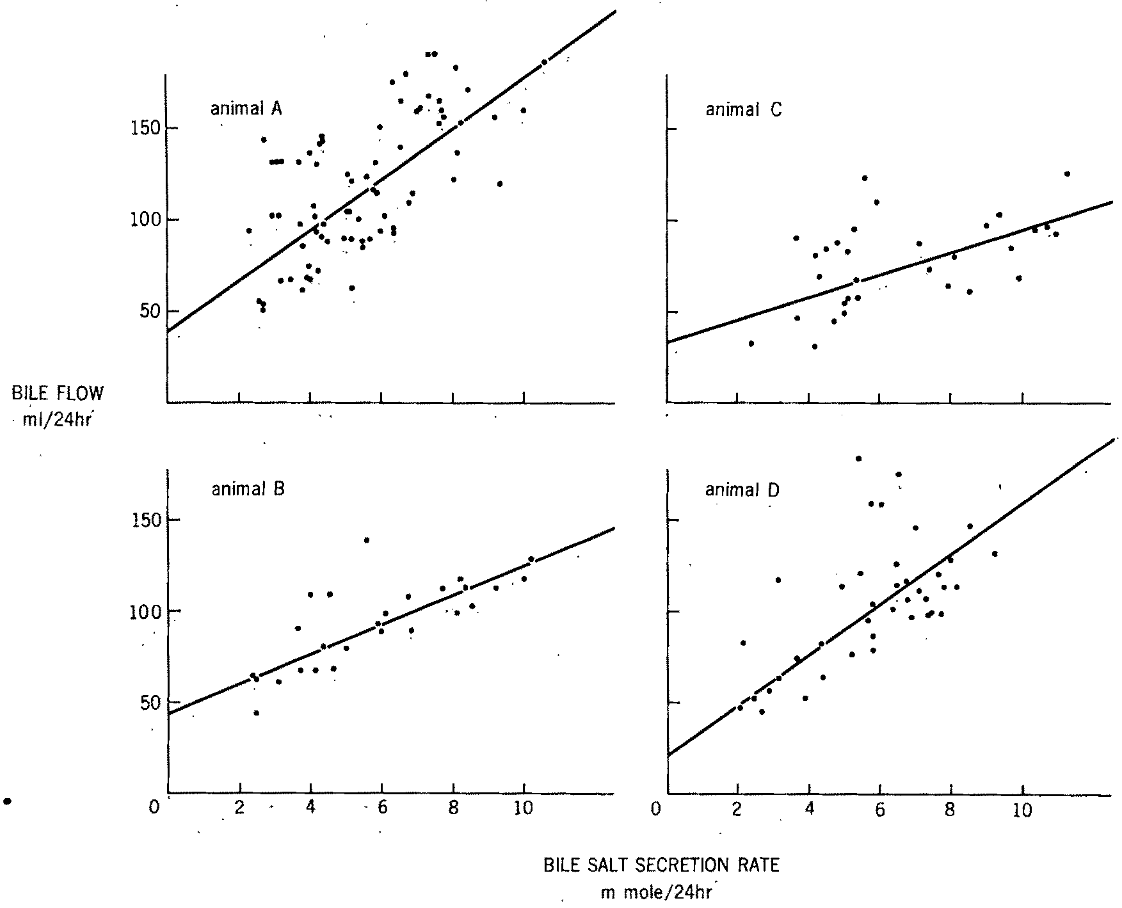

FIG. 3. Fasting experiment. Bile flow vs bile salt secretion rate in samples obtained from animals receiving intraduodenal monkey bile infusions. Line shown is linear regression line.

TABLE 3. *Fasting Experiments: Linear Regression Data and Standard Error of the Estimate (Measure of Scatter) During Sodium Cholate, Sodium Taurocholate and Bile Infusions*

Infusion		A	B	C	D	E
Sodium Cholate	Slope	7.57	12.72	11.54	12.19	20.54
	Y intercept	64.15	34.44	20.57	23.41	14.41
	Linear correlation coefficient ("r")	.479	.815	.760	.865	.896
	p for "r"	<0.001	<0.001	<0.001	<0.001	<0.001
	Standard error of the estimate (S.E.E.)	26.53	15.72	29.22	14.43	21.92
Sodium Taurocholate	Slope	—	—	7.68	11.58	8.84
	Y intercept	—	—	29.60	15.98	35.85
	Linear correlation coefficient ("r")	—	—	.567	.932	.784
	p for "r"	—	—	<0.05	<0.001	<0.001
	Standard error of the estimate (S.E.E.)	—	—	19.32	10.00	21.42
Bile	Slope	13.76	8.12	6.25	14.25	—
	Y intercept	39.11	44.34	33.12	20.42	—
	Linear correlation coefficient ("r")	.674	.778	.611	.760	—
	p for "r"	<0.001	<0.001	<0.001	<0.001	—
	Standard error of the estimate (S.E.E.)	27.44	14.37	20.98	24.75	—

coefficients of the comparable fasting experiments ($p < 0.01$).

The mean bile salt independent flow (Y-axis intercept) was larger in the feeding experiment than in the comparable fasting experiment, in the same animal. Because there was very little fluctuation in bile flow at any bile salt secretion rate, the bile salt independent flow in each sample must have been very close to this mean. The reduction in the vertical dispersion from the linear regression line is indicated by the S.E.E., which was four to five times less than the comparable fasting values obtained during sodium cholate infusions. The difference was significant ($p < 0.01$). These results demonstrate that frequent small feedings result in an increased and stabilized bile salt independent flow.

TABLE 4. *Feeding Experiment: Bile Flow and Bile Salt Secretion Rate on Three Successive Days During Sodium Cholate Infusion*

Day	Infusion	Bile Flow	Bile Salt Secretion Rate
1.	6 mmoles/24 hr sodium cholate	218.4	7.7
		216.0	7.7
		201.6	6.3
		201.6	6.8
		198.4	6.6
		190.4	6.8
		211.1	7.6
2.	4 mmoles/24 hr sodium cholate	193.6	5.7
		194.4	5.9
		172.8	5.2
		182.4	5.3
		187.2	5.9
		182.4	5.4
		176.0	5.8
3.	Saline	116.4	1.5
		109.2	1.3
		122.4	1.5
		111.6	1.4

Note constancy of bile flows and close relationship between changes in bile salt secretion rate and change in bile flow (Animal A).

Conjugation of Bile Salts. Findings were similar to the fasting experiments.

Discussion

The pertinent observations in this experiment may be summarized as: 1) Bile flow is linearly related to the bile salt secretion rate in both fasted and fed primates; 2) Bile salt independent flow is extremely variable in fasted primates, during infusions of conjugated and unconjugated bile salts, or bile; and 3) Bile salt indepen-

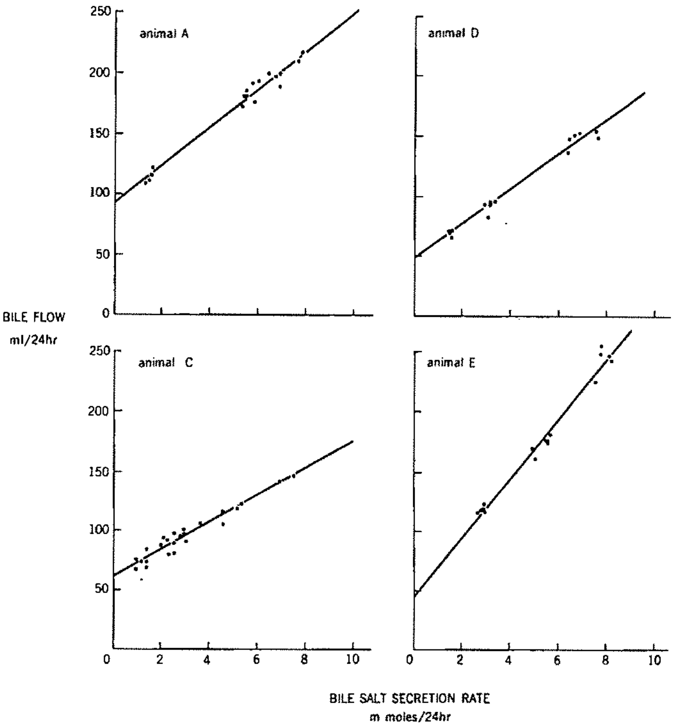

FIG. 4. Feeding experiment. Bile flow vs bile salt secretion rate in samples obtained from animals receiving intraduodenal sodium cholate infusions. Line shown is linear regression line.

TABLE 5. *Feeding Experiments: Linear Regression Data and Standard Error of the Estimate During Sodium Cholate Infusions*

		A	B	C	D	E
Infusion Sodium Cholate	Slope	16.10	—	11.45	14.51	24.61
	Y Intercept	92.64		60.90	48.66	45.33
	Linear Correlation Coefficient ("r")	.988	—	.966	.989	.988
	p for "r"	<0.001	—	<0.001	<0.001	<0.001
	Standard Error of the Estimate S.E.E.	4.95	—	5.30	5.55	7.44

Note high correlation coefficients and small standard errors compared to data in Table 3.

dent flow is increased and stabilized by steady feeding.

The following explanations of the differences in experimental findings described in the introduction may be made, as a result of the observations in the present experiment. Wheeler[12] found that bile flow fluctuated at one bile salt secretion rate in the fasted dog, not receiving anticholinergic agents. This result is similar to our own in fasted primates. No attempt to correlate bile flow to bile salt secretion was made under these conditions in the dog, although, as shown above, significant correlation does exist in the fasted primate, despite considerable dispersion of the data. Instead, anticholinergic agents were administered to the dogs and bile flow was stabilized.[6] The anticholinergic agent used (Piptal, Lakeside Laboratories) completely suppresses gastric acid secretion.[3] The latter is a potent stimulant of secretin release from the duodenum,[12] which in turn stimulates bicarbonate rich ductular secretion.[7] Bicarbonate secretion in the bile was considerably reduced when Piptal was used,[6,12] suggesting that the stabilization of bile flow at one bile salt secretion rate was achieved by suppression of bile salt independent flow, originating from the bile ductules. This is further supported by examination of the linear correlation data between bile flow and bile salt secretion in the dogs receiving Piptal.[6] There is little dispersion of the data points from the linear regression lines and the Y-axis intercepts are close to zero, indicating that there is little or no bile salt independent flow. Since Wheeler[6] obtained stabilization of bile flow by suppressing bile salt independent flow, and Dowling[2] used a fed animal in which bile salt independent flow is high and stable (confirmed by our experiments), one must conclude that the difference in bile flow at low bile salt secretion rates in these two experiments is not due to species variation, but to the use of a fasted model receiving an anticholinergic agent, by Wheeler, and to the use of a fed model by Dowling.

Nahrwold[5] found significant bile flow in fasted dogs at low bile salt secretion rates. This would be expected since anticholinergic agents were not used. This finding is similar to our own in fasted primates. There was a much larger bile flow at low bile salt secretion rates in fed dogs, a finding similar to Dowling's experiments[2] and the present experiments in fed primates.

Finally, there is Nahrwold's interesting observation that fasted dogs given an intraduodenal bile infusion do not respond with an increase in bile flow, although the bile salt secretion rate by the liver rises.[5] This finding appears to contradict Wheeler's,[6] Dowling's[2] and our own conclusion that there is always linear correlation between bile flow and the bile salt secretion rate. However, the intraduodenal bile infusion was associated with a large decrease in the hepatic bicarbonate output,[5] indicating that the ductular secretion of bile was inhibited by the intraduodenal bile infusion. It is not surprising that the ductular bile salt independent flow would decrease under these conditions since the release of secretin is dependent on a low pH and the bile that was infused into the duodenum would have had a slightly alkaline pH. Wheeler's demonstration that alkalinization of the duodenum may be associated with a drop in bicarbonate output and bile flow,[12] supports this. It is likely that, in Nahrwold's experiment, the increase in bile salt secretion was indeed associated with an increase in the bile salt dependent flow, but that this was offset by a decrease in the bile salt independent flow, so that total flow remained unchanged. This explanation was first suggested by our own fasting experiments in which there are numerous examples of samples having the same bile flow at different bile salt secretion rates. This is due to the fact that total flow in a sample with a small bile salt dependent flow and a large bile salt independent flow, may equal total flow in a sample with a large bile salt dependent and a small bile salt independent flow.

The combined infusion of food and bile in Nahrwold's experiment was associated with an increase in flow and bicarbonate output. Obviously, the addition of food more than compensated for the inhibiting effect of alkaline bile infusion on ductular flow.

The results of the present experiment may be useful in planning studies of bile formation, especially in abnormal states such as biliary tract obstruction. Food intake must be similar in control and experimental periods of a study, if the changes found are to be attributed to factors other than food intake. Sometimes, this may be difficult when drugs affecting appetite are given or when the animal is made uncomfortable (eg. biliary tract obstruction).[9] Fasting for prolonged periods may itself affect composition and is therefore not acceptable.[8] The use of intestinal intubation to provide stable food intake throughout the experiment may be a suitable method of overcoming this problem. Recently, we have studied the effect of repeated intermittent biliary tract obstruction.[10] The animals were fed at 8 A.M., during both the control and experimental periods. In the experimental period, the animal was obstructed from 6 P.M. to 8 A.M. and allowed to recover from obstruction from 8 A.M. to 6 P.M. The animals ate equally well during control and experimental periods, since obstruction was relieved just prior to feeding. We were able to compare control and experimental bile flows during similar periods of the day using this technique.

Anticholinergic agents have been very useful in stabilizing bile flow so that relationships between bile flow and bile salt secretion could be analyzed.[6] These drugs should probably be avoided, except for this specific reason, since they eliminate bile salt independent flow, which may be a desirable parameter to investigate. Also, it has not been clarified whether anticholinergic agents have other undesirable effects, eg. on bile composition.

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A Technique for Estimating the Position of the Oxygen-Hemoglobin Dissociation Curve

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A nomogram was constructed which allows estimation of the P_{50} value from the Po_2 and per cent O_2 saturation of a single venous blood sample. There was excellent correlation between 50 estimated P_{50} values obtained in 27 severely ill patients when compared with P_{50} values determined from constructed OH-DC's (correlation coefficient 0.92). The mean of the differences between the estimated and determined P_{50} values was 1.5 mm Hg with a standard deviation of ±1.1, and the maximum difference was 4 mm Hg.

THE TRANSPORT OF OXYGEN from the body's external environment to its peripheral tissues depends on several factors, including the concentration and partial pressure of oxygen in the inspired air, alveolar ventilation, ventilation-perfusion relationships, cardiac output, blood volume, and hemoglobin concentration. The recent demonstrations that the level of organic phosphates in the red blood cell has a significant effect on the position of the oxygen-hemoglobin dissociation curve (OH-DC) have served to focus attention on the processes responsible for *release* of oxygen at the tissue level.[4,6] The position of the OH-DC describes the affinity of hemoglobin for oxygen, and influences the transfer of oxygen from blood (hemoglobin) to tissue cells.

In a complex clinical setting, multiple factors that influence hemoglobin-oxygen affinity may be present; and abrupt changes in the position of the OH-DC may occur secondary to the disease process or therapy. Evaluation of these multiple influences may be difficult, since little data concerning their cumulative effects is available. However, their *net* effect can be estimated by determining the position of the OH-DC. The P_{50} value indicates the position of the OH-DC, and is defined as the oxygen tension, in mm Hg, at 50% hemoglobin saturation with oxygen.

A P_{50} value is normally obtained by constructing an OH-DC by one of several standard techniques, which are time-consuming and not readily available in most hospitals. With the knowledge that the shape of the OH-DC does not change appreciably with changes in the position of the curve, a method for estimating the P_{50} value from the oxygen tension (Po_2) and O_2 saturation of a sample of venous blood has been developed. The purpose of the present study was to compare P_{50} values obtained by this method (estimated P_{50}) with the P_{50} values determined by construction of an OH-DC (determined P_{50}).

Methods

Fifty separate measurements of estimated and determined P_{50} values were made from venous blood samples drawn at random from 27 acutely ill or injured patients in the Trauma Research Unit, the Surgical Intensive Care Unit and the Burn Care Unit at Parkland Memorial Hospital, Dallas, Texas. The patients ranged in age from 16 to 78 years with a mean age of 47 years. There were 20 males and 7 females. Repeat studies on individual patients were performed at least 24 hours apart. Blood samples for the determined and estimated P_{50} values were drawn anaerobically from the superior vena cava

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or a femoral vein into separate heparinized syringes. P_{O_2} and pH measurements were made with an Astrup apparatus, and the O_2 saturations were measured on an American Optical Oximeter. All measurements were performed in duplicate and the values were averaged.

Estimated P_{50}

A nomogram was prepared to allow an estimation of the P_{50} from the P_{O_2} and O_2 saturation values of a sample of venous blood (Fig. 1). The nomogram consists of a set of OH-DC's aligned in parallel along the P_{O_2} axis. A standard OH-DC ($P_{50} = 27$ mm Hg) at pH 7.4, temperature 37 C, and P_{CO_2} 40 mm Hg was drawn using the computed subroutine of Kelman.[9] This subroutine is based on a mathematical model of the OH-DC similar to that proposed by Adair.[2] It allows the development of OH-DC's at different positions on the P_{O_2} axis according to changes in pH, temperature, or P_{CO_2} by use of the equation:

$$P_{O_2}(\text{expected}) = P_{O_2}(\text{normal}) \times 10^{[0.024(37-\text{temp})+0.40(\text{pH}-7.40)+0.06(\log 40-\log P_{CO_2})]}$$

where P_{O_2} (normal) is the P_{O_2} on the standard OH-DC.[7] Sequential increases in pH by units of 0.1 from pH 6.8 to 7.9 were used to produce the positional alignments of a group of curves around the standard OH-DC.

Each estimated P_{50} value was obtained by plotting the point on the nomogram which represented the measured P_{O_2} and O_2 saturation of a fresh venous blood sample. The OH-DC upon which this point fell was followed to its intersection with the line of 50% O_2 saturation. The P_{O_2} at this point represented the P_{50} value (Fig. 1). If the point fell between two OH-DC's, an imaginary line parallel to the nearest OH-DC was followed to its intersection with the line of 50% O_2 saturation. The P_{50} value was determined at the patient's venous pH, and was corrected to the patient's temperature using the factor suggested by Severinghaus.[15]

Determined P_{50}

The determined P_{50} values were obtained by constructing an OH-DC by a standard mixing chamber technique. A heparinized venous blood sample was divided into two 10 ml portions. In an Instrumentation Laboratories 137 Mixing Chamber, one sample was exposed to an atmosphere of 95% O_2 and 5% CO_2, while the other was exposed to a mixture of 95% nitrogen and 5% CO_2. After a 15 minute equilibration period, each of three syringes were filled anaerobically with different proportions of blood from each chamber. The O_2 saturation in these syringes approximated 45%, 60% and 70%. The pH, P_{O_2} and O_2 saturation of each sample were measured within 10 minutes after removal of the blood from the chamber. A point representing the P_{O_2} and (% O_2 saturation/100-% O_2 saturation) for each of the three mixtures was plotted on log-log graph paper and a regression line (representing the OH-DC) was fitted to the three points by the least squares method.[8] The determined P_{50} value obtained from this OH-DC was corrected to the patient's venous pH and the measured body temperature using correction factors suggested by Severinghaus.[15]

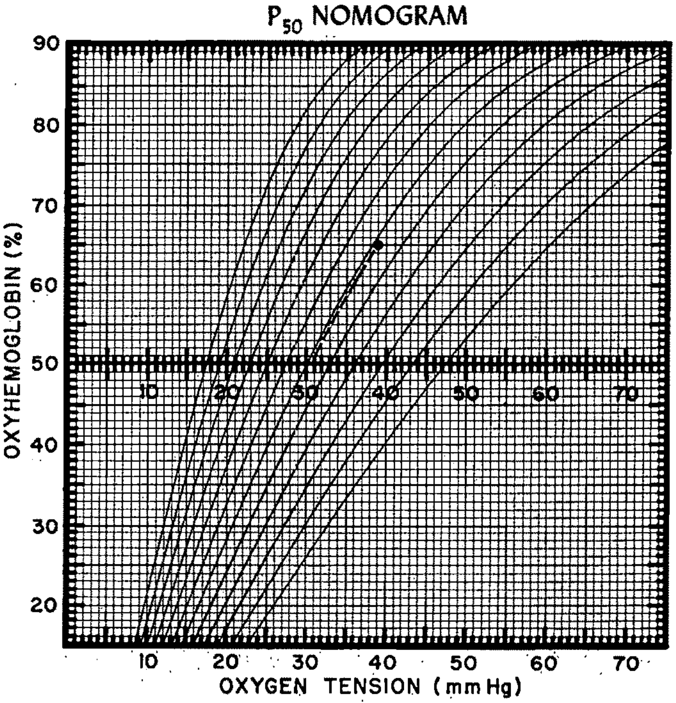

FIG. 1. Nomogram for estimation of P_{50} value (position of the oxygen-hemoglobin dissociation curve). The point on the nomogram corresponding to the measured P_{O_2} and saturation of a sample of venous blood is traced to the line representing 50% oxygen saturation. This intersect represents the estimated P_{50} (normal value approximately 27 mm Hg). Example: venous blood sample P_{O_2} = 39 mm Hg, oxygen; saturation = 65%; P_{50} value = 31 mm Hg. (A rightward position dissociation curve.)

Results

The determined P_{50} values ranged from 22 to 42 mm Hg. Thirty of the estimated P_{50} values were below the corresponding determined P_{50}, 18 were above and 2 were the same. The correlation coefficient between the two sets of P_{50} values was 0.92 with a P value <.001 (Fig. 2). The differences between the determined and estimated P_{50} values ranged from 0 to 4 mm Hg, with a mean difference of 1.5 mm Hg and a standard deviation of ±1.1 mm Hg.

Discussion

The OH-DC reflects the interaction between oxygen and hemoglobin, and both the shape and position of the curve are subject to change. The most common alteration

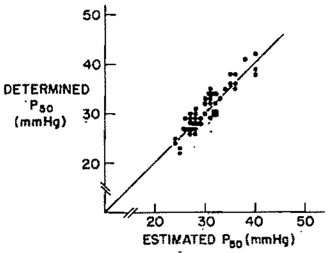

FIG. 2. Comparison between estimated P_{50} values and the determined P_{50} values in 27 acutely ill patients (50 sets of determinations. Correlation coefficient = 0.92, P value = <0.001).

is a change in the affinity of hemoglobin for oxygen as indicated by a change in the position of the OH-DC along the P_{O_2} axis. Variations in pH, temperature, carbon dioxide tension, and the concentration of organic phosphates are the most frequent causes of altered hemoglobin-oxygen affinity encountered in the clinical setting. The other factors known to effect the position of the OH-DC have been summarized recently by Shappel and Lenfant (Table 1).[16]

Within limits, rightward or leftward shifts of the OH-DC have little effect on arterial oxygen saturation if the arterial P_{O_2} is above 80 mm Hg. At the peripheral capillary level, however, even small shifts of the OH-DC may be important. A rightward shift of the OH-DC (P_{50} above 27 mm Hg) indicates decreased hemoglobin affinity for oxygen, while a leftward shift (P_{50} below 27 mm Hg) indicates an increase in hemoglobin-oxygen affinity. A rightward shift of the OH-DC is advantageous theoretically, since an equivalent amount of oxygen is released at a higher P_{O_2} than with a leftward positioned curve.[16]

Since alterations in hemoglobin-oxygen affinity occur in many disease states,[5,10,11,13,14,17,18,20] a knowledge of the position of the OH-DC (P_{50} value) may be important in the care of seriously ill patients. The conventional methods for measuring the P_{50} are probably too time consuming for clinical use. However, the results of the present study indicate that an estimate of the P_{50} value can be made with reasonable accuracy from the measured P_{O_2} and O_2 saturation of a single sample of venous blood. In our group of patients, there was good correlation between the estimated and determined P_{50} values (correlation coefficient—0.92), with an average difference between the two determinations of 1.5 mm Hg and a maximum difference of 4 mm Hg.

INCREASE P_{50}	DECREASE P_{50}
By Direct Effect:	*By Direct Effect:*
Increased $[H^+]$	Decreased $[H^+]$
Temperature	Temperature
P_{CO_2}	P_{CO_2}
DPG, ATP	DPG, ATP
Hgb. Conc.	Hgb. Conc.
Ionic Strength	Ionic Strength
Abnormal Hemoglobin	Abnormal Hemoglobin
Aldosterone	Carboxyhemoglobin
	Methemoglobin
By Increasing DPG:	*By Decreasing DPG:*
Decreased $[H^+]$	Increased $[H^+]$
Thyroid hormone	Decreased thyroid hormone
Pyruvate kinase deficiency	Hexokinase deficiency
Increased inorganic phosphate	Decreased inorganic phosphate
Cortisol	Cell age (old)
Cell age (young)	

Adapted from: Shappell, S.D. and Lenfant, C.J.M.: Adaptive, Genetic and Iatrogenic Alterations of the Oxyhemoglobin-dissociation Curve. *Anesthesiology*, 37:127-139, 1971.

TABLE 1. *Factors that alter hemoglobin-oxygen affinity.*

Because of the sigmoid shape of the OH-DC, it is important that the O_2 saturation of the blood sample used for P_{50} estimation fall on the steep portion of the curve. The error in estimating the P_{50} value increases rapidly when the O_2 saturation is above 75% or below 25%. The O_2 saturation of the majority of venous blood samples fall within this range, but the high saturation of most arterial blood samples preclude their use for P_{50} estimation.

Accurate measurements of P_{O_2} and O_2 saturation are essential, since small errors in these determinations can result in large errors in the estimated P_{50}.[1] Although P_{O_2} values between 0–150 mm Hg can be measured with consistent accuracy,[3,12] the error of O_2 saturation measurements increases as the per cent saturation falls.[19] In order to minimize the errors during P_{50} estimation, the O_2 saturation of the venous blood sample ideally should be between 40% and 75%. When blood samples with O_2 saturations outside this range are used, the expected error must be considered when evaluating the P_{50} value.

Although the nomogram was originally developed to simplify the P_{50} estimation, it has proved to be a useful teaching aid to facilitate a conceptual understanding of the P_{50} value. The estimated P_{50} values may also be calculated from the measured P_{O_2} and O_2 saturation of a venous blood sample using the Severinghaus formula:

$$\text{Estimate } P_{50} = 26.6 \times \frac{P_{O_2}}{P_{O_2\,SAT}}$$

in which P_{O_2SAT} is the P_{O_2} on the standard OH-DC corresponding to the measured O_2 saturation.[1] Alternately, this calculation can be made using the Severinghaus Blood Gas Calculator*.[15] The measured P_{O_2} and O_2 saturation of the blood sample are aligned on Scale A and Scale B respectively. The estimated P_{50} is that P_{O_2} on Scale A immediately above the point of 50% O_2 saturation on Scale B.

Generally, the P_{50} value is corrected to a standard pH and temperature. However, correction to the patient's pH and temperature probably results in a more realistic approximation of the *in vivo* P_{50} value. As described in this report, the P_{50} estimate is measured at the patient's venous pH. However, most devices designed to measure P_{O_2} bring the blood sample to a temperature of 37 C or 38 C prior to the determination. If the patient's temperature differs significantly from this value, it is desirable to correct the P_{50} value using the factor suggested by Severinghaus,

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*Blood Gas Calculator, Type BGC-1 (Scales designed by J. W. Severinghaus, M. D.), Copyrighted 1967 by Radiometer A/S, Emdrupve, '72, Copenhagen NV, Denmark.

$$\Delta \log P_{O_2} = 0.031\ \Delta\,\text{temp.}$$

or with the Severinghaus Blood Gas Calculator.[15]

The use of estimated P_{50} values has become routine in our care of critically ill patients. Combined with measurements of both arterial and venous blood gases, a considerable amount of information may be obtained regarding the state of oxygenation and oxygen transport capability.

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Addendum

Since preparation of this manuscript, the Radiometer Blood Gas Calculator (Type BGC-1)® has been modified to calculate the P_{50} value from the measured PO_2 and O_2 saturation of a sample of venous blood. Use of the calculator also allows for simultaneous correction of the P_{50} value to the patient's temperature, pH, and base excess.

New Observations in the Clinical Spectrum of the Budd-Chiari Syndrome

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Some observations on the natural history, surgical management and metabolic phenomena in B.C.S. are presented. In one patient side to side portocaval shunt brought dramatic improvement with asymptomatic followup of 5 years. The patient died of causes unrelated to B.C.S. At postmortem the shunt was patent and normal liver architecture was preserved. The second patient presented with a fulminant course culminating in acute hepatorenal syndrome. There was marked hypofibrinogenemia and extreme elevation of SGOT. Emergency portocaval shunt was followed by marked improvement in liver status. The patient died of respiratory complications on the 8th postoperative day. The third patient is one year on conservative treatment only and well. In this patient excessive renal tubular reabsorption of sodium at a distal site was documented. This may explain the generalised edema formation in patients with B.C.S. even without inferior vena cava obstruction. This is apparently the first reported instance of renal tubular function studied in B.C.S.

THROMBOSIS of the hepatic veins—Primary Budd-Chiari Syndrome (BC.S.)—presents itself with hepatomegaly and the accumulation of ascites. The course of the disease is variable from patient to patient. In some, the evolution of the disease is slow and the patient can be maintained on conservative treatment. On the other hand, some patients with BC.S. may present with rapidly accumulating refractory ascites and fulminating liver failure leading to death. The course of the disease and the outcome in a given patient is difficult to predict. There is no unanimity in the literature concerning the optimal management of patients with the BC.S.[7]

The purpose of the present communication is to describe our experience in the management of three patients with BC.S. and to report some new clinical and laboratory findings in this syndrome.

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Case Reports

Patient No. 1. This patient has been reported previously from this institution[4] and the present communication is a followup report. She had initially presented with rapidly accumulating ascites due to hepatic vein occlusion. An emergency portocaval shunt was constructed in an attempt to decompress the liver. The postoperative improvement was dramatic: the tendency to fluid retention subsided and she required no diuretic therapy. Repeated liver function tests were normal. After five years of normal life the patient died of a brain abscess apparently unrelated to her liver disease. At postmortem the liver weighed 1800 gm. The portocaval shunt was patient with a normal portal venous system. The cause of death was an abscess in the left parietal lobe of the brain.

Microscopic examination at postmortem showed that the normal liver architecture was preserved. There was severe widespread sinusoidal congestion but no fibrosis. Almost all the hepatic veins were occluded by organised thrombi. Some small branches of the hepatic veins were converted to solid fibrotic cords. The congestion was less severe than in the biopsy specimens of five years ago (Fig. 1).

In the light of the postmortem finding, it appears today that the early fibrosis seen in the postoperative biopsies (Fig. 6 & 7 in ref. 4) was within the hepatic vein. It did not develop into parenchymal fibrosis as had been suggested in the previous publication.

Comment

This patient apparently represents one of the very few with longterm followup to be reported. The outcome suggests that portocaval shunt operation may prevent destruction of the liver by severe congestion.

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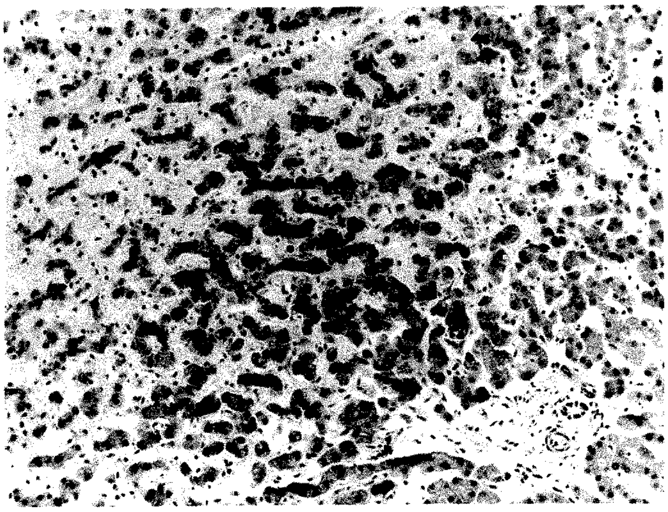

FIG. 1. Patient No. 1: Section of the liver at postmortem. Marked sinusoidal dilatation in the central portion of the lobule. The portal tract is normal. There is no evidence of fibrosis in the liver (× 100, H. & E. stain).

Patient No. 2. On Feb. 23, 1972, a 41-year-old woman was admitted to another hospital because of shock. One month before this illness she had a bout of diarrhea. The history was otherwise noncontributory; the patient did not use oral contraceptives. The liver was enlarged, but liver function tests were reported as normal. On Feb. 25, 1972, the patient was transferred to the Department of Nephrology at this center because of anuria. She was obtunded with a normal blood pressure. The liver was massively enlarged and the abdomen distended by ascites. There was a suspect lump in her left breast. There was no engorgement of the jugular veins in the neck and the E.C.G. showed low voltage. Blood chemistry revealed: SGOT activity of 2700 units (normal less than 40), profound hypofibrinogenemia (80 mg%). Alkali phosphatase 3.2 B.L. units (normal 2.6 or less), bilirubin 3.4 mg%, total proteins 5.2 g% with an even ratio of albumin and globulin. The blood ammonia was slightly elevated (93 μg%). Hepatic venous outflow obstruction was tentatively diagnosed and caval catheterisation performed. During this study the patency of the inferior vena cava was demonstrated. There was no manometric evidence of constrictive pericarditis. Some of the hepatic veins were occluded, others grossly narrowed. The diagnosis of primary hepatic vein thrombosis was, therefore, established. The ascites was aspirated and peritoneal dialysis instituted because of continuing renal shutdown. Exploratory laparotomy was performed on Feb. 27, 1972. Approximately 4 l of transudate was present in the abdominal cavity. The liver was enlarged, hard and had a blueish mottled appearance. The veins of the G.I. tract were grossly engorged. The portal vein pressure was 24 cm of water with a simultaneous systolic arterial pressure reading of 80 mm Hg. The portal pressure fell to 14 cm of water when the liver side of the puncture was clamped but rose to 32 cm of water when the mesenteric side was occluded. During the operation severe "sweating" of the whole region of the liver was observed; therefore, a side-to-side portocaval shunt was established lowering the portal pressure to a sustained level of 16 cm of water. In the days following the operation there was marked improvement in liver function. No ascites accumulated since the operation. The SGOT activity fell to 150 units and serum fibrinogen concentration rose to 180 mg/100 ml units. There was a rise in the serum bilirubin to 12.2 mg%, and a fall in total proteins to 4.4 g%, mostly due to albumin loss. Blood ammonia was normal. Because of persistent renal shutdown the patient was hemodialised repeatedly. On the 6th postoperative day she developed bronchopneumonia and died on the 8th postoperative day, despite intensive antibiotic treatment and positive pressure respiration.

The liver biopsy performed at the laparotomy and before the porto-systemic shunt was established, showed the typical picture of BC.S.: the normal architecture was preserved. There was severe congestion of the central vein and sinusoids, involving the inner half of each lobule. The portal tracts were normal and some of the hepatic vein branches were occluded by fresh thrombi. In others, there was fibro-elastic thickening of the intima (Fig. 2).

At postmortem examination the liver was enlarged and congested. The two main hepatic veins and most of the smaller veins were occluded by fresh thrombi. The histology of the liver showed extreme sinusoidal congestion and necrosis of approximately two-thirds of the inner part of each lobule (Fig. 3). The large hepatic veins were occluded with recanalised thrombi. The kidneys were enlarged and pale. They showed increased thickening of the cortex and medulla. The parenchyma was edematous and of soft consistency. The medulla appeared hyperemic. The glomeruli and blood vessels appeared normal. There was severe hydropic swelling of the proximal convoluted tubuli with few hyaline casts in their lumina. The arcuate veins were congested. There was a mild degree of round cell infiltration around the large veins and around some collecting ducts. The entire picture was compatible with acute tubular necrosis.

Comment

The course in this patient demonstrates the extreme rapidity with which the liver damage can progress in cases with acute BC.S. Both clinical and biochemical features were fulminating. Surgical decompression appeared to improve the liver functional profile.

Patient No. 3. A 41-year-old housewife was admitted in March 1972 because of upper abdominal pain associated with abdominal distension. For the past eighteen years she has been known to suffer from cholelithiasis with infrequent attacks of upper abdomi-

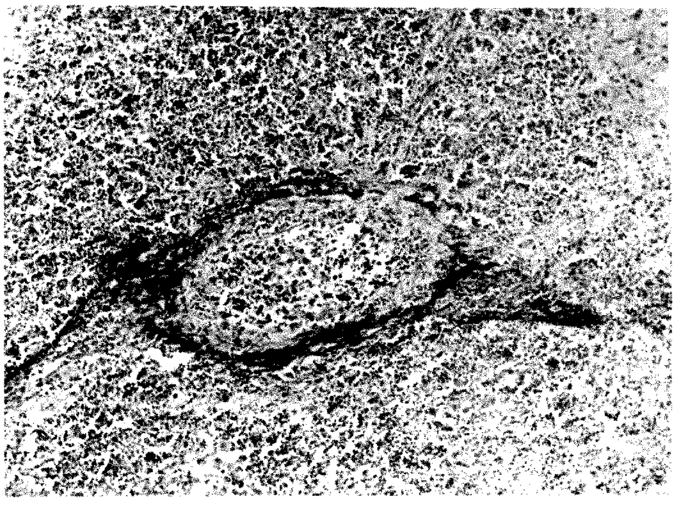

FIG. 2. Patient No. 2: Intraoperative biopsy. A sublobular vein shows thickening of intima and occlusion of the lumen by thrombotic mass. Around the vein there is marked sinusoidal congestion. Almost no liver parenchyma can be recognized in this portion of the liver (× 100 Weigart Elastic stain).

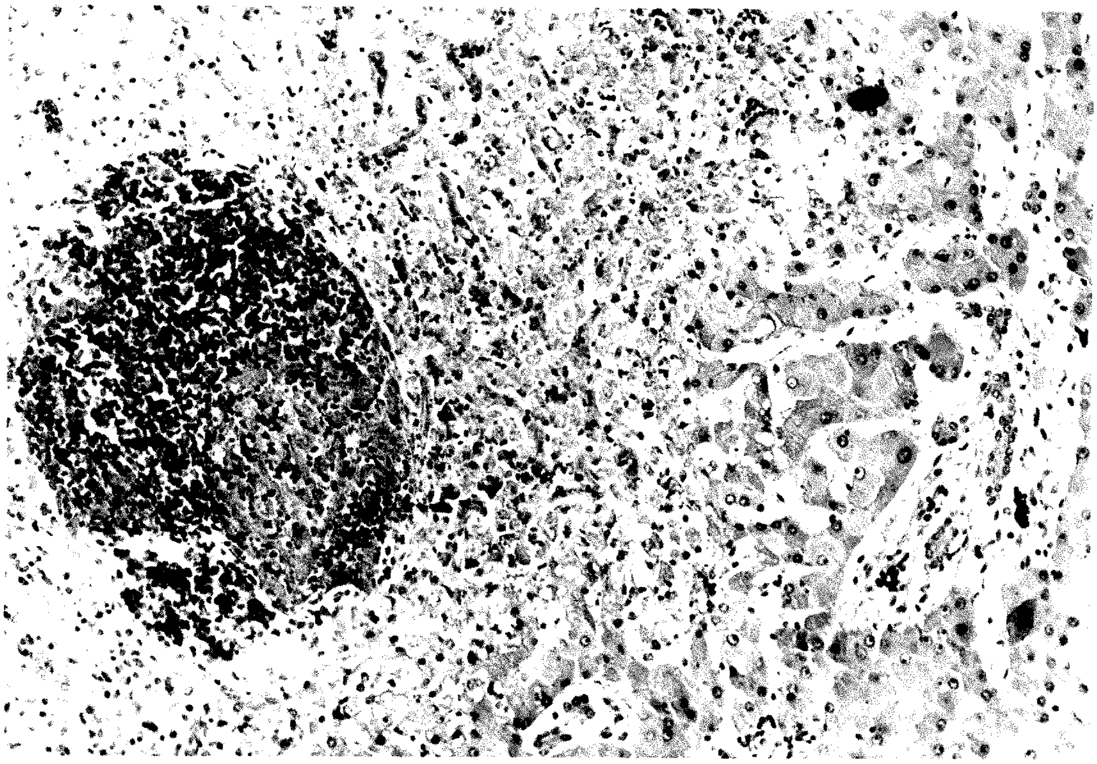

FIG. 3. Patient No. 2: Postmortem. Portion of a liver lobule with dilated central vein occluded by a fresh thrombus. Around the veins there are congested sinusoids and necrotic liver cells. At the periphery there is a normal portal tract surrounded by remnants of viable hepatic cords (× 250, H. & E. stain).

nal pain. The presence of gall stones was confirmed radiologically. Cholecystectomy was suggested to the patient but operation was refused.

Over the past year she complained of frequent attacks of colicky upper abdominal pain associated with flatulence. There had been no jaundice, weight loss, anorexia, vomiting or diarrhea. For three weeks previous to admission she observed a progressive swelling of the abdomen as well as swelling of the ankles.

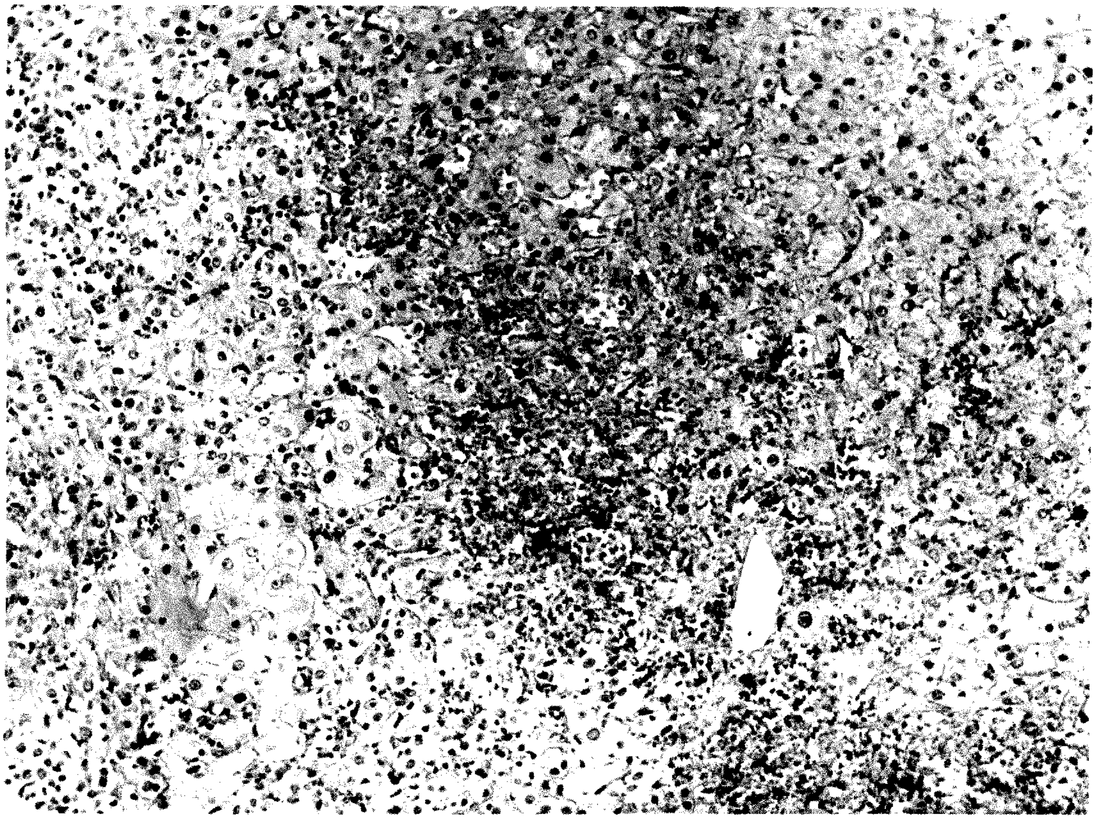

FIG. 4. Patient No. 3: Intraoperative biopsy of the liver. The central portion of the lobule shows congestion of sinusoids with disappearance of hepatocytes (× 250 H. & E. stain).

On examination she appeared ill, the blood pressure was 160/90, she was minimally jaundiced. The abdomen was distended and ascites was present. There was tenderness in the epigastric region and right upper quadrant. The liver was enlarged 10 cm below the costal margin and was firm, tender and irregular. The spleen was palpable 4 cm below the costal margin. Venous markings were exaggerated over the abdominal wall and blood flow in them appeared away from the liver. Pitting edema was present over both legs.

The hemoglobin was 16.5 g%; leukocytes 10,000 pcmm with a normal differential count. The prothrombin time varied between 18% and 40% of the control. Platelet count was normal. Urinalysis was normal. The serum bilirubin varied 1.2–3.0 mg/100 ml. The highest SGOT level recorded was 37 international units. The serum alkaline phosphatase varied 2.8–4 Bessi-Lowrie units. Total serum proteins 6.9 g% with globulin 3.7 g% and albumin 3.2 g%. Several bromsulfalein retentions after 45′ were from 5%–20%. The ascitic fluid was clear, straw colored with a protein content of 1.8 g%. It was sterile and no abnormal cells detected. The fibrinogen level was 466 mg%. Bleeding time and clotting time were within normal limits. Radiology of the gastro-intestinal tract was normal apart from the presence of oesophageal varices. The gallbladder did not fill on either oral or intravenous cholecystography. Inferior vena cavogram revealed a patent vena cava. On selective hepatic vein catheterisation only one patent vein could be demonstrated. Liver scan was noncontributory. On liver needle biopsy there was chronic congestion consistent with BC.S.

On April 18, 1972, laparotomy was performed. The liver was enlarged, grossly congested and macronodular. Portal pressure measured through the gastro-epiploic vein was 30 cm of H_2O. Portovenography revealed a patent portal system. The gallbladder wall was thickened with signs of chronic cholecystitis and the gallbladder was full of stones. The cystic and common bile ducts were free of stones. Cholecystectomy was performed. No pathology was noticed around the inferior vena cava and portal vein. Liver biopsy at the time of operation confirmed the diagnosis of BC.S. and showed marked sinusoidal dilatation in the central half of each lobule with disappearance of liver cells in this area. The portal tracts were of normal size and shape.

The postoperative course was uneventful. The treatment consisted of daily administrations of furosemide and aldactone. Over a followup period of one year, she has remained free of ascites and peripheral oedema. The liver and spleen have not changed in size or consistency and liver function did not deteriorate.

Kidney function tests performed on June 5, 1972, showed: Inulin clearance (C_{IN}) was 76.7 ml/min, PAH clearance (C_{PAH}) was 269.9 ml/min, filtration fraction (C_{IN}/C_{PAH}) was 0.25. Maximal urinary osmolality following 24 hours of water deprivation was 550 mos/Kg (normal: more than 800 mos/Kg), urea excretion was 18 g/24 h. Maximal free water reabsorption (T_{H_2O}) was 6.6 ml/min 100 ml GFR (normal). Free water clearance (C_{H_2O}) during sustained oral water load was 14.3 ml/min/100 ml GFR (normal). Minimal urinary osmolality was 60 mos/Kg. The fraction of distally delivered sodium reabsorbed at the diluting site $C_{H_2O}/(C_{H_2O} + C_{Na})$ was 99.3% (normal mean 83.3 ± 3.6%). The laboratory methods of this tests and their interpretation were previously reported from this institution.[2,3]

Comment

The slow and benign course in this patient may be attributable to the degree of hepatic vein occlusion and the insiduousness of its progression.

Since sodium reabsorption at the diluting site was supra-normal and maximal free water absorption in the collecting duct was normal, the defect in maximal concentration cannot be explained by a defect in sodium reabsorption or impermeability of the collecting duct to water in the presence of A. D. H. By exclusion, washout of medullary hypertonicity appears to underlie the defect in urinary concentration in this patient.

Discussion

The three patients described demonstrate the great variability of the clinical pattern in BC.S. In patients No. 1 and 2 the course was fulminant and rapid. Within a few weeks after the onset of discomfort the patients presented with massive hepatomegaly and ascites. Furthermore, in patient No. 2 there were also profound disturbances in hepato-cellular function and acute renal failure. Such a course is most probably due to rapid occlusion of the total hepatic venous outflow. In contrast to this finding there is the slow more benign course in patient No. 3 which can probably be attributed to the patency of one hepatic vein.

It is interesting to note that in patients No. 1 and 3, SGOT and fibrinogen levels were normal. Normal values in these two parameters were also found in most patients reported in a previous large series.[8] It appears, therefore, that elevation of SGOT and fall in fibrinogen level may be a danger signal which should alert consideration of emergency surgical decompression of the liver.

The favorable longterm course following portocaval shunt in patient No. 1 as well as in a few similar case reports[5] proves that in man the portal vein can replace the hepatic venous outflow. The postmortem finding in the liver of this patient suggests that the human liver adjusts well to this diversion of venous blood and that the damage due to venous congestion is not self perpetuating once the congestion is relieved. The immediate reversal of abnormalities in liver function following P.C.S. in patient No. 2 supports this assumption.

Renal tubular function has not been previously studied in man in hepatic vein obstruction. In patient No. 3 we found that there was a defect in maximal urinary concentration. This defect could not be explained on the basis of malnutrition, reduced delivery of sodium to the diluting segment nor was it attributable to impermeability of the collecting ducts to water. It is speculated that the diminished concentrating ability in this patient with BC.S. is due to wash-out of renal medullary hypertonicity secondary to enhanced medullary blood flow. In contrast to the impairment in urinary concentration, urinary diluting capacity was normal in patient 3. This suggests that the site of excessive tubular reabsorption of sodium is distal to the proximal tubule. The reason why venous congestion in the liver interferes with tubular handling of sodium is not clear. It appears, however, that excessive tubular reabsorption of sodium underlies the tendency for generalised edema formation in patients with BC.S. Edema in the legs, therefore, may have its cause in early renal sodium retention in acute BC.S. and need not necessarily be due to inferior vena cava obstruction. A similar defect in urinary concentration as described above has been found in cirrhosis[5] and in dogs with chronic bileduct obstruction.[1]

The benign course in patient No. 3 on conservative treatment only stresses the importance of assessing each patient on an individual basis. A carefully controlled trial of conservative treatment should probably be attempted in most patients with BC.S.

There were some metabolic abnormalities in our patients which to the best of our knowledge have not been reported previously. Patient No. 2 presented with severe hypofibrinogenemia. This raised the suspicion that the patient suffered from disseminated intravascular coagulation. However, the normal thrombocyte count as well as the normal level fibrin degradation products suggested reduced fibrinogen production by the liver as the cause of hypofibrinogenemia.

The human liver may adapt to slow partial obstruction of the hepatic venous outflow. However, sudden and complete occlusion of hepatic veins cause rapid deterioration of hepatic cell function. Side-to-side porto-systemic shunting seems to be the only chance of preserving the viability of the liver in this condition. Extreme deterioration of liver function, elevation of SGOT and probably hypofibrinogenemia may be the indications for active-operative treatment.

Addendum

After submission of this manuscript, patient No. 3 became jaundiced and the ascites refractory. This occurred some 20 months after her first admission. Progression of the hepatic vein thrombosis was diagnosed. The patient was advised to undergo immediate operative decompression of her liver, but declined.

Her condition deteriorated and on April 2, 1974 she was admitted in profound hepatic coma and massive G.I. bleeding. An emergency portocaval shunt operation was attempted but the patient died shortly after this procedure.

At postmortem the liver was small, nodular and extremely congested. The hepatic vein that had previously been patent was now completely occluded. The portocaval anastomosis was found to be thrombosed.

The course in this patient stresses the grave dangers facing patients with BC.S. and emphasizes the importance of an early aggressive approach in every patient with BC.S. whose liver function begins to deteriorate.

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Letters to the Editor

Dear Editor:

The Anglem and Leber paper (The Dubious Case for Conservative Operation in Operable Cancer of the Breast. Ann. Surg., Nov. 1972, p. 625) was a direct attack on my published figures and on those of several others who have written in support of conservative operations, but none of us had an opportunity of reviewing the paper before it was published. Anglem and Leber's article contained no original material that had not been previously reported. Its comments on my results and on those of Dr. Vera Peters and of Drs. Brinkley and Haybittle contained many inaccuracies. Quotations were lifted out of context to give false interpretations. Information that was necessary to interpret the comparisons was often withheld. Anglem and Leber's article also compared the Cleveland Clinic's observed and unadjusted 10-year survival rate with their own survival rate based on "definitive cases," in which patients lost to followup or dying of causes other than cancer were not counted. They also compared selected patients from individual surgeons' private practices with our unselected institutional experience involving all patients in all stages of breast cancer. Furthermore, they compared results in our patients, classified by Manchester Staging, with those obtained in the favorable groups of the Columbia Presbyterian Staging. Finally, they consistently considered only patients treated by radical mastectomy, disregarding those who because of age, disability, or extent of disease were considered to be inoperable. The results that were obtained in this favorable group they compared with those in our Manchester Stages I and II that included all patients in all stages except those in the hopelessly incurable Stages II and IV.

The fact of the matter is that the 10-year survival rate of the Cleveland Clinic's Manchester Stage I and II patients treated without radical mastectomy is identical (42% to 43%) with that reported in the National Cancer Registry, in which the patients were treated predominantly by radical mastectomy.

Dr. Anglem's attack was rebutted in detail in the Fall edition of the American Cancer Society's Journal, CA.

Copies of an even more detailed rebuttal are available on request to anyone who wishes to write me for one.

Sincerely yours,

George Crile, Jr., M.D.
Cleveland Clinic
Dept. of General Surgery
9500 Euclid Avenue
Cleveland, Ohio 44106

Dear Editor:

In a discussion of such a controversial subject as the choice of treatment for operable cancer of the breast, critical analysis of the data presented by proponents of one side of the question cannot reasonably be considered an attack on the individuals whose material has been reviewed. We do not consider our critique of the case for conservative surgery an attack on Dr. Crile or on any of the other authors whose data have been analyzed. Our purpose was simply an attempt to assess the validity of some of the claims made for conservative treatment and of the statistics offered in their support.

Our comments on the evidences of bias in the form of favorable case selection in Crile's and Peter's published reports are accurate and based on their own reported figures and can be fully documented. With respect to the Brinkley and Haybittle paper we might also have pointed out that of their unfavorable Stage II cases, 77% were allocated for treatment by radical mastectomy and only 23% by local excision.

Dr. Crile's statement that we have compared Cleveland Clinic's observed and unadjusted 10-year survival rate with our own survival rate based on "definitive cases" in which patients lost to followup or dying of causes other than cancer is false and completely without foundation.

In our own original paper we reported our 10-year survival rate for Columbia Stage A and B patients operated on between 1949 and 1959 as 60%. In response to

Dr. Crile's original rebuttal we supplied our figure for all operable patients in Columbia Stages A, B, and C of 57%, in round numbers. In this calculation all patients dying of causes other than cancer were considered dead of cancer. In this series we had one patient lost to followup. Excluding this case, our 10-year survival rate was 57.28% and including it, 56.73%.

Since Dr. Crile has seen fit to raise this issue it may not be inappropriate to remind him that in two recent publications reporting his results following local excision, he has excluded from consideration a number of patients totalling in each instance 6% of the cases reported for reasons completely inadmissible by generally accepted standards of end result reporting.

Dr. Crile's suggestion that our clinical material is superior to his because our patients are encountered in a private rather than an institutional practice and because of his use of the Manchester classification versus our use of the Columbia classification is totally unacceptable. In fact, the reverse is true. A far more reliable indication of the quality of clinical material is the average size of the tumors in the respective series. Dr. Crile reports the average diameter of the tumors in his patients treated by simple mastectomy as 2.5 cm. Ours, for all operated cases from 1949 to 1959, is 3.2 cm. This difference is far greater than it appears at first glance. If the tumors may be considered roughly spherical, the volume of a tumor 3.2 cm in diameter is more than double that of one with a diameter of 2.5 cm.

Dr. Crile's statement that we have consistently considered only patients treated by radical mastectomy, disregarding those who because of age, disability or extent of disease were considered inoperable, is meaningless. Of course we did, since we are discussing only operable cancer of the breast. The same is true of his operated cases which are all in Stage I and II which by definition are operable, as indicated in the table below modified from one of his recent publications.

Cleveland Clinic

All Patients 1957–1964 Inclusive	501
Operable Stage I and II	401
Inoperable from other causes Stage I & II	8 Inoperable
Stages III and IV	101 Inoperable

Finally, Dr. Crile's comparison of his 10-year survival rate for his patients treated without radical mastectomy with that reported in the National Cancer Registry for patients treated predominantly by radical mastectomy is again a comparison of a highly selected group with a series that is totally unselected. Crile's patients treated without radical mastectomy constitute a series containing a great preponderance of Stage I cases and having an average diameter of only 2.5 cm and from which the more advanced and unfavorable Stage II cases have been screened out and allocated for treatment by his radical operation.

Copies of our response to Dr. Crile's detailed rebuttal will also be available on request to anyone who wishes to write for one.

Sincerely yours,
Thomas J. Anglem, M.D.
Robert E. Leber, M.D.
110 Francis Street
Boston, Massachusetts 02215

Books Received

Munster, Andrew M., Thomas, George J.: *Surgical Anatomy for Clinical Examination,* C. C Thomas, Publisher, Springfield, Illinois, 1973, $10.75.

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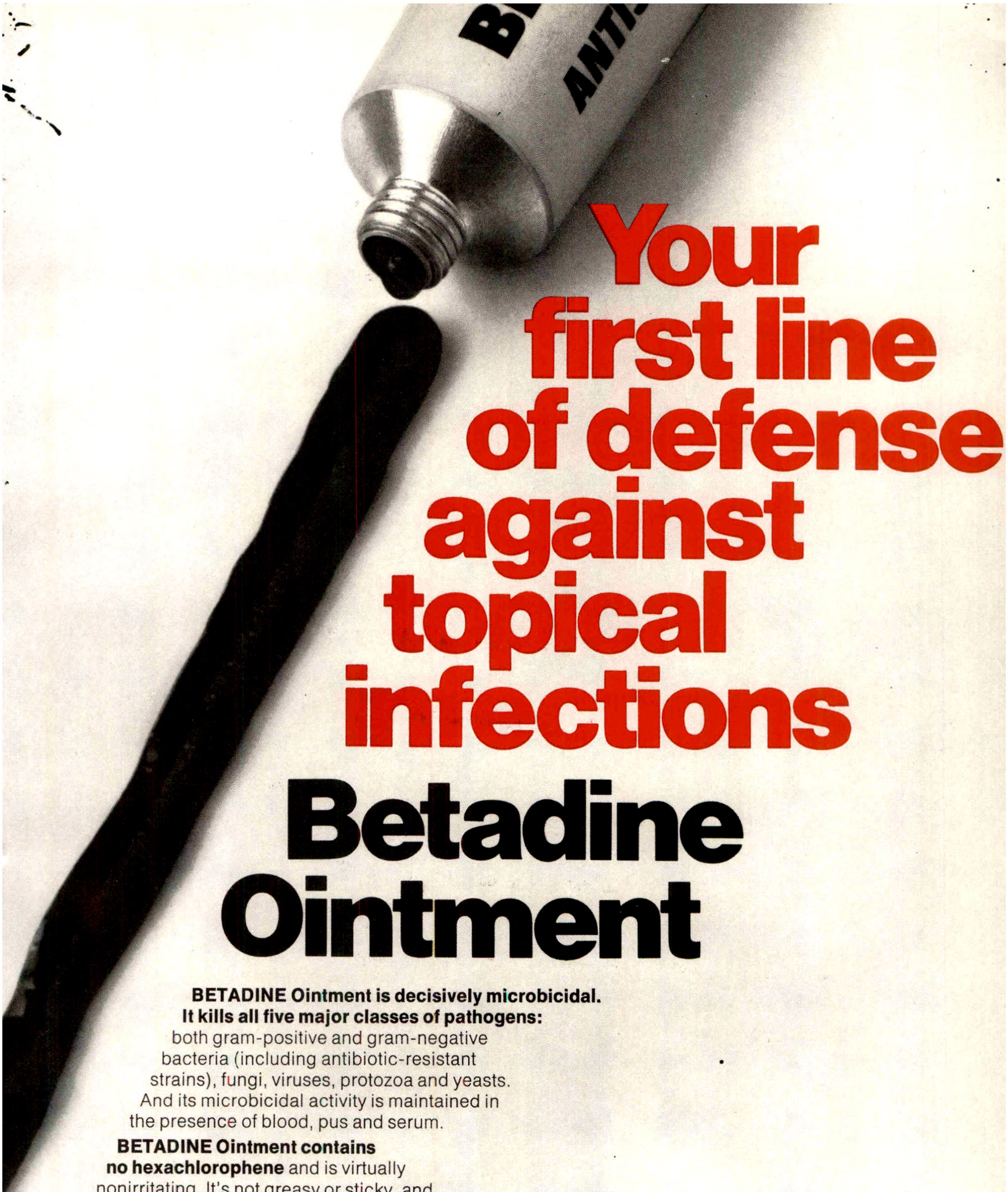

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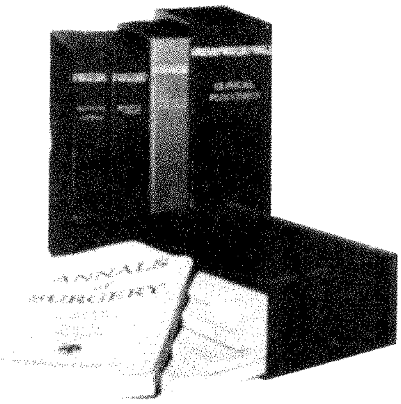

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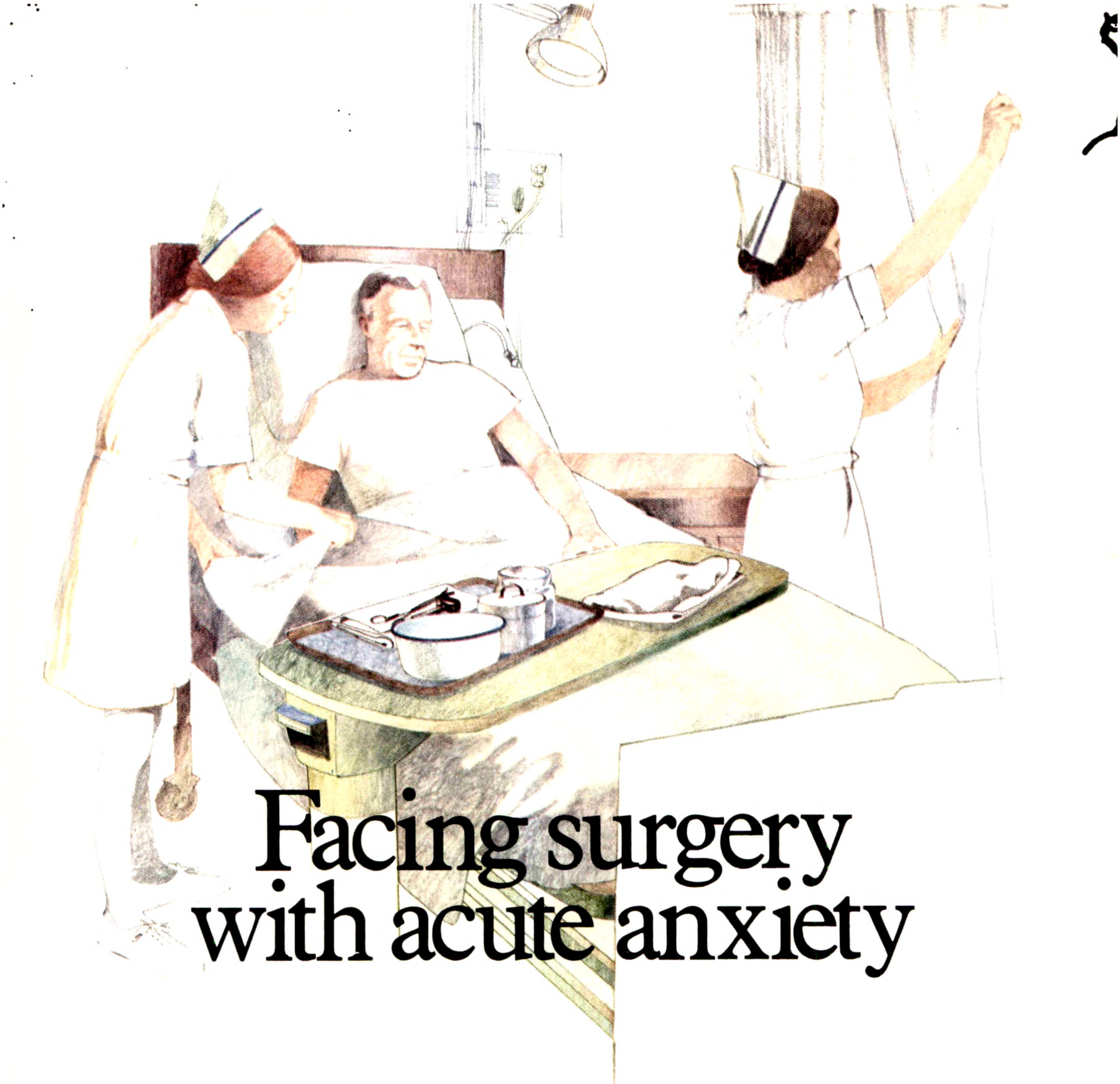

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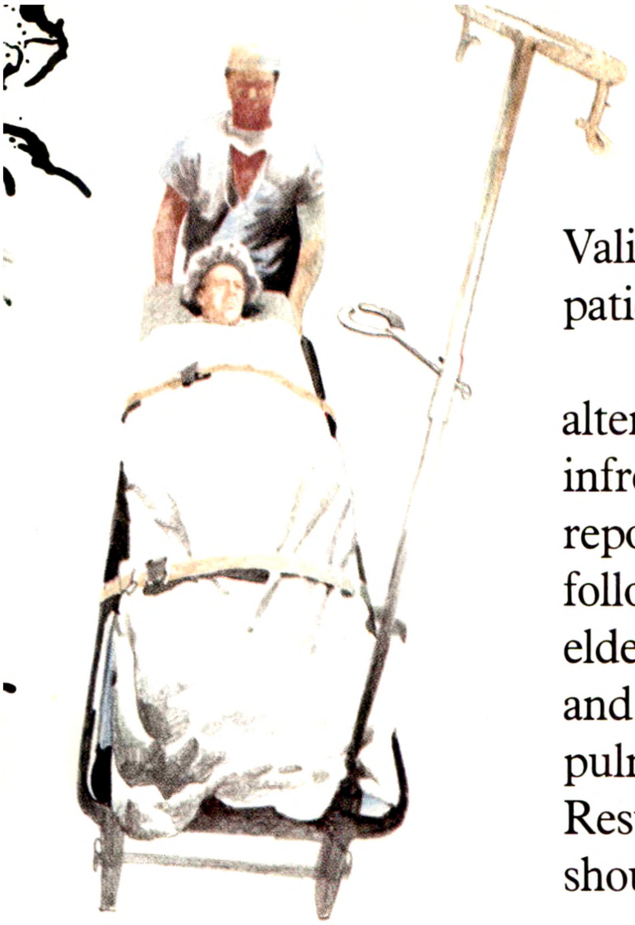

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Contraindicated: In infants; in patients with known hypersensitivity to the drug; in acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *When used I.V., the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment. Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Administer with extreme care to elderly or very ill and those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; have resuscitative facilities available. When used with narcotic analgesic eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, nursing women or women of childbearing potential, weigh expected benefit against possible hazard to mother and child. Not recommended for OB use.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm and increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic and have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly and debilitated; safety and efficacy in children under 12 not established.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis and phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 min. prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma and diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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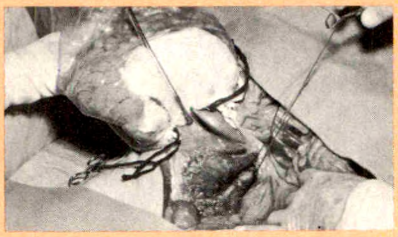

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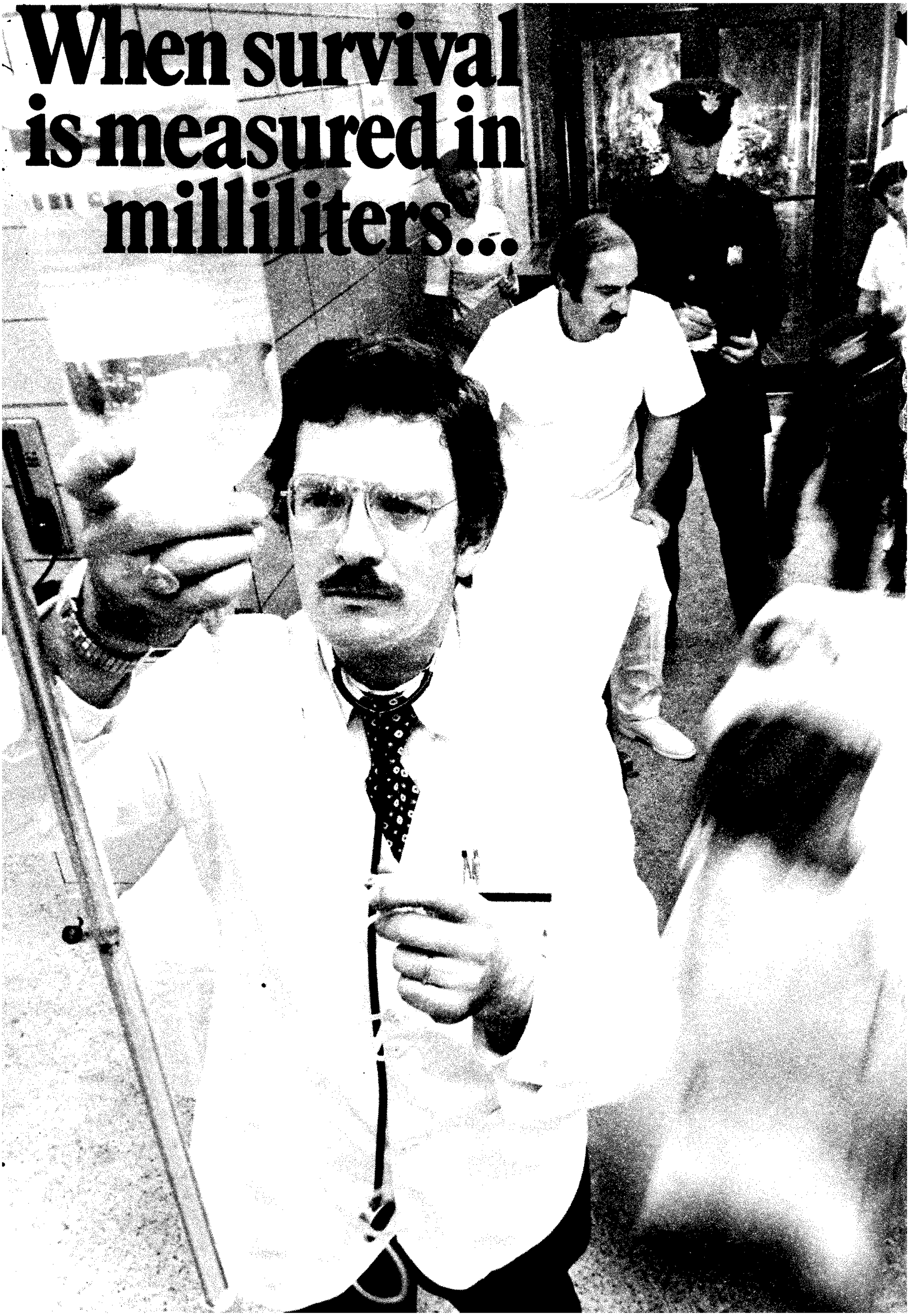
When survival is measured in milliliters...

Moments and milliliters... both are critical in treating hypovolemic shock since survival depends on the rapid, efficient restoration of circulating blood volume. Also crucial is the volume expander you use "stat." Rheomacrodex starts to work immediately to restore blood volume and adequate tissue perfusion.

Greater Initial Plasma Volume

In a recent study,[1] plasma volume expansion and cardiac output were measured in 36 patients with moderate or severe degrees of shock and in eight healthy subjects before, during and after infusion with 500 ml 10% dextran 40, whole blood, 6% dextran 70, plasma, and 5% dextran 40. The greatest plasma volume expansion was established in the 24 shock patients treated with Rheomacrodex. Peak plasma volume increases were more than one liter above controls. Plasma volumes decreased slowly as urinary output increased. Other studies also show the superiority of Rheomacrodex over blood, plasma, saline or lactated Ringer's for increasing initial plasma volume.[2-5]

Improved Cardiac Output

Measurement of hemodynamic effect revealed increased cardiac output directly related to increased volume expansion. Peak C.O. values occurred 15 minutes after Rheomacrodex infusion. In patients with moderate or severe degrees of shock, 10% dextran 40 increased cardiac output an average of 70% above control values.[1] Rheomacrodex improves hemodynamics – restores effective cardiac output and tissue perfusion – better than whole blood, plasma or clinical dextran.

Increased Tissue Perfusion

Restoring blood pressure often is not enough to reverse shock. Most important is the maintenance of adequate tissue perfusion. Rheomacrodex achieves this by decreasing red blood cell aggregation to a greater extent than crystalloids, blood or plasma.[6-10] This improvement in microcirculatory blood flow is reflected in increased oxygen availability and consumption, a vital contribution to the reversal of shock.[11]

Delayed Renal Excretion

In hypovolemia, delayed renal clearance tends to prolong the colloid osmotic effects of Rheomacrodex.[1] During infusion, Rheomacrodex is evenly distributed in the vascular system. The plasma concentration of dextran falls rapidly during the first hour as smaller molecules are excreted. Generally, 70% of Rheomacrodex infused in normovolemic subjects is excreted via the kidney in 24 hours.[12] Excretion is then slowed as the higher molecular weight fraction of dextran remains in the circulation to be metabolized at the rate of 70-90 mg/kg body weight per 24 hours.

Guidelines for Use

1. May be administered on a "response to therapy basis" up to 1,500 ml initially in first 24 hours.
2. Infuse first 500 ml within 30 minutes.
3. To support blood volume beyond 24 hours, administer 500 to 1,000 ml daily.
4. Do not continue beyond five days.
5. May be given with whole blood.
6. Keep patient well hydrated. Increase hydration if urine flow drops below 50 ml/hour.
7. Can be given to any patient without blood typing. However, blood should be drawn prior to infusion for future testing.

REFERENCES: **1.** Shoemaker, W.C. and Monson, D.O.: Surg. Gynec. Obstet. 137:453. 1973. **2.** Ahnefeld, F.W. et al.: Anaesthesist 14:137 (May) 1965. **3.** Gelin, L.E. et al.: Acta Chir. Scand. 122:309, 1961. **4.** Gruber, U.F. et al.: Proc 10th Cong Int Soc Blood Transf., 1965, pp. 1116-1119, S. Karger, Basel (Switzerland). **5.** Gruber, U.F. et al.: Symposium on Rheomacrodex I (1964), pp. 13-23. **6.** Mainardi, L.C. et al.: Surgery 56:349 (Aug.) 1964. **7.** Martinovic, N. and Melrose, D.: J. Cardiovasc. Surg. 4:610 (Aug.) 1963. **8.** Suzuki, F. et al.: Ann. Surg. 160-263 (Aug.) 1964. **9.** Baker, R.J. et al.: Arch. Surg. 90:538 (Apr.) 1965. **10.** Baker, R.J. et al.: Arch. Surg. 89:373 (Aug.) 1964. **11.** Mohr, P.A. et al.: Circulation 39:379 (1969). **12.** Arturson, G. and Wallenius, G.: Scand. J. Clin. Lab. Invest. 16:81, 1964.

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(dextran 40)

For greater blood volume...faster

CONTRAINDICATIONS: Hypersensitivity to dextran. Marked hemostatic defects of all types. Marked cardiac decompensation. Renal disease with severe oliguria or anuria.

WARNINGS: Severe and fatal anaphylactoid reactions may occur infrequently during the early part of the first infusion of dextran. If such reactions appear imminent, stop infusion mmediately. Since dextran draws water from extravascular space, give dehydrated patients dditional fluids (degree of dehydration can be assessed by serum or urine osmolarity). uretics may be used to maintain adequate urine flow. Renal failure, sometimes irreversible, motic nephrosis, and, occasionally, abnormal hepatic and renal function values have been ported. Because safety in early pregnancy has not been established, do not use in women of ldbearing age unless potential benefits outweigh risks. Use cautiously in patients with ve bleeding.

CAUTIONS: Doses up to 15 ml/kg may produce small changes in coagulation; factor VIII decrease markedly, but bleeding time is only rarely prolonged significantly. Observe all nts for early signs of bleeding complications. Monitoring of central venous pressure may void circulatory overloading. Do not depress hematocrit below 30 vol. %. Dextran erence with blood glucose determinations, some blood typing and cross matching procedures and bilirubin and protein assays can be avoided by drawing blood samples pri giving Rheomacrodex or by informing lab that Rheomacrodex has been given so that suital assay methods can be used.

ADVERSE REACTIONS: Hypersensitivity reactions, which occur infrequently, can range fro mild cutaneous eruptions to generalized urticaria, nausea and vomiting, tightness of the c wheezing, and, rarely, to anaphylactoid (allergic) shock. If any such reactions appear, start appropriate countermeasures promptly.

DOSAGE: Total dosage should not exceed 20 ml /kg in the first 24 hours or 10 ml/kg in eac subsequent 24 hours. Do not continue beyond 5 days.

SUPPLIED: Bottles of 500 ml 10% solution in normal saline or in 5% aqueous dextrose.

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INDICATIONS: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS: *Drug Dependence:* Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Percodan, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, Percodan is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Percodan should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Percodan may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Percodan should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children: Percodan should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical oourse of patients with head injuries.

Acute abdominal conditions: The administration of Percodan or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: Percodan should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS: The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. The usual adult dose is one tablet every six hours as needed for pain.

DRUG INTERACTIONS: The CNS depressant effects of Percodan may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE: *Signs and Symptoms:* Serious overdose with Percodan is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of Percodan may, in addition, result in acute salicylate intoxication.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

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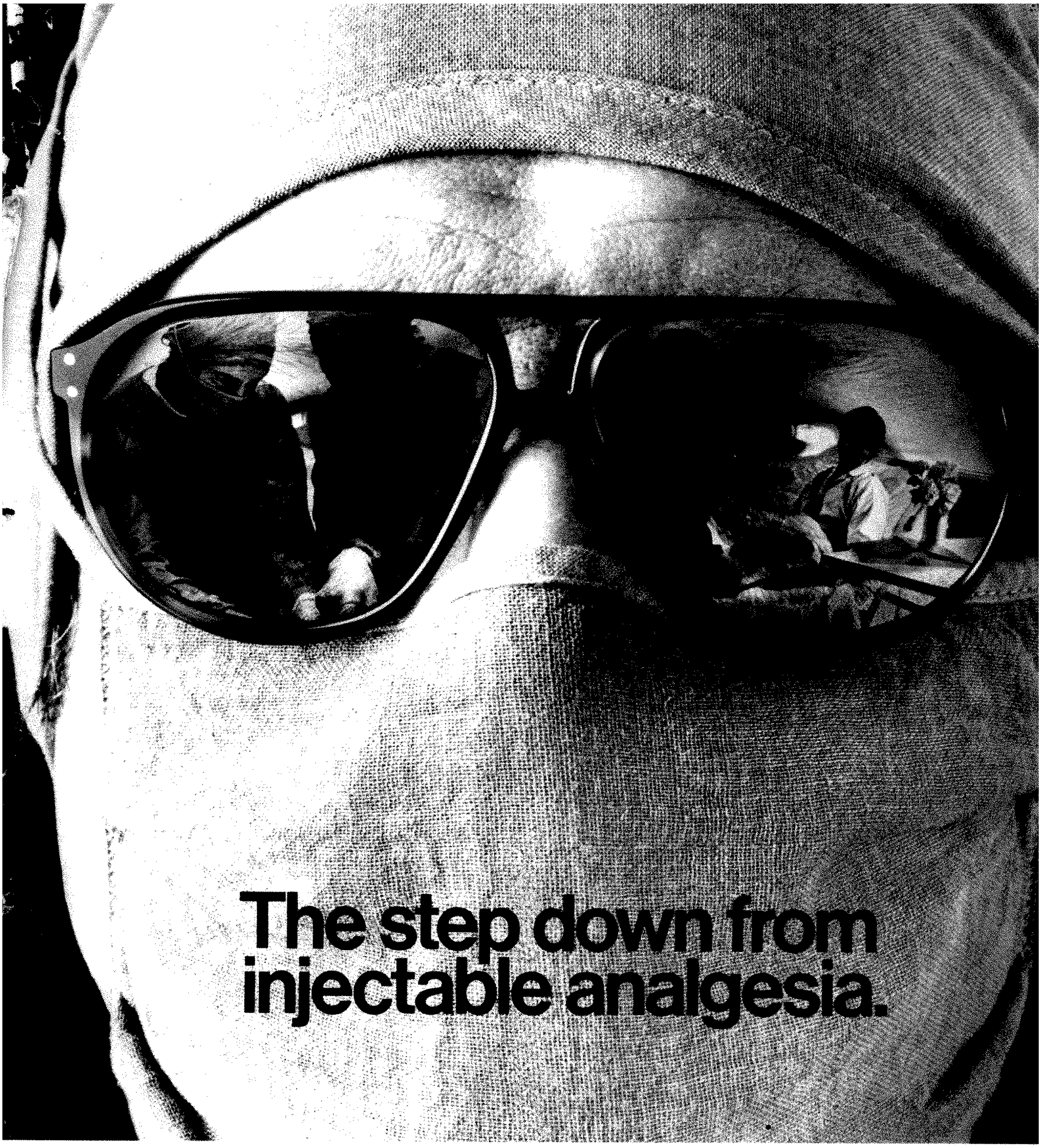
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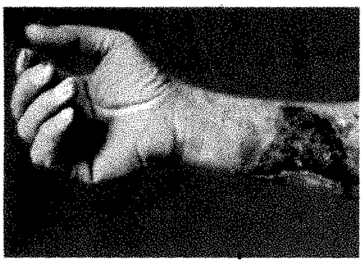

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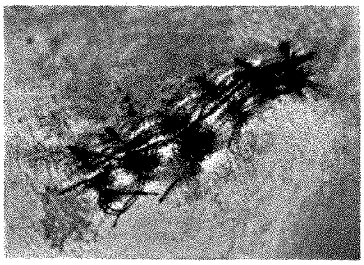

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